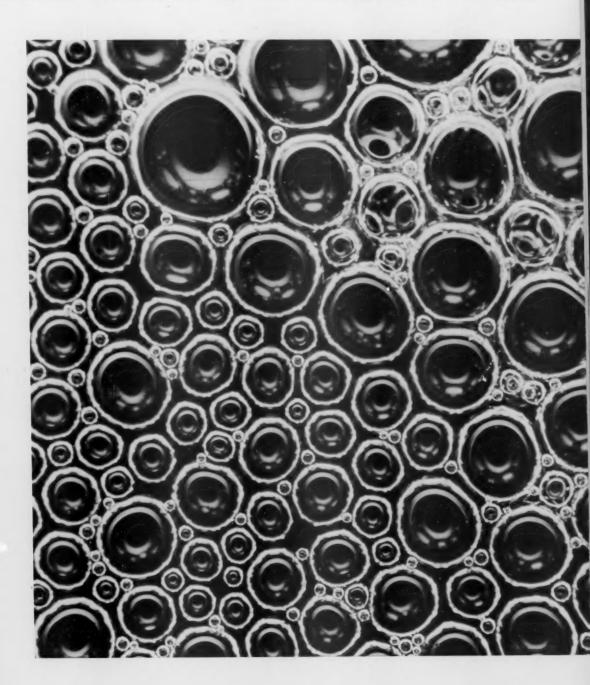
# SCIENCE 1961 Vol. 134, No. 3489

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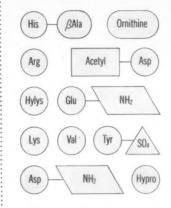
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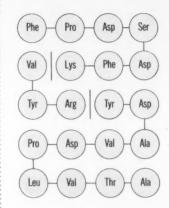
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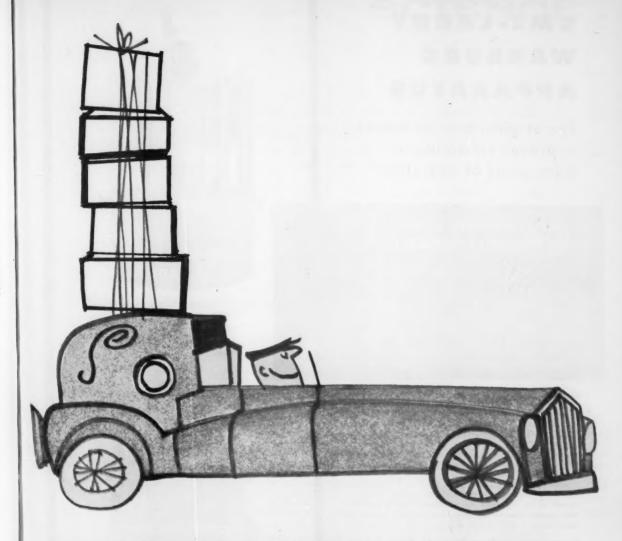
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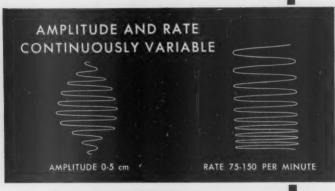
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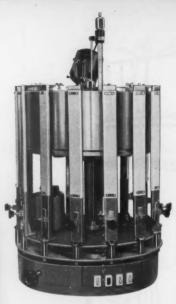
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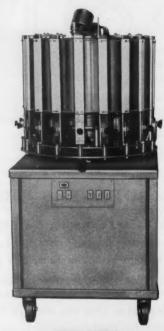
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# SCIENCE

Editorial	"Say It Ain't So"	1493
Articles	Pathways of Intracellular Hydrogen Transport: G. E. Boxer and T. M. Devlin  Absence of enzymatic hydrogen-carrying systems is a factor in aerobic glycolysis of malignant tissue.	1495
	Cause and Effect in Biology: E. Mayr  Kinds of causes, predictability, and teleology are viewed by a practicing biologist.	1501
	Physiological Implications of Laser Beams: L. R. Solon, R. Aronson, G. Gould  The very high radiation flux densities of optical masers point to important biomedical applications.	1506
Science and the News	The Next Budget: The President Is Saying a Few Things He Cannot Really Believe; Soviet-American Exchanges: For Different Reasons, Both Sides Find Them Advantageous	1509
Book Reviews	Science Survey, reviewed by W. Sullivan; other reviews	1514
Reports	Cerebral Dysfunction and Intellectual Impairment in Old Age:  H. Misiak and A. W. Loranger	1518
	Humming: A Vocal Standard with a Diurnal Variation: L. Rubenstein	1519
	Localized Cooling in the Brain: V. H. Mark et al.	1520
	Functional Effects of Focused Ultrasound on Mammalian Nerves:  R. R. Young and E. Henneman	1521
	Gonadotrophic Hormones Affect Aggressive Behavior in Starlings: S. F. Mathewson	1522
	Localization of Carbonic Anhydrase in the Nervous System: E. Giacobini	1524
	Ocular Lesions Produced by an Optical Maser (Laser): M. M. Zaret et al	1525
	Oral Proline Tolerance in Osteogenesis Imperfecta: G. K. Summer	1527
	Longevity of Fusarium oxysporum in Soil Tube Culture: C. D. McKeen and R. N. Wensley	1528
	Photoperiodic Response of an Albino Mutant of Einkorn Wheat in Aseptic Culture: M. Sugino	1529
	Genetical and Geographic Studies on Isoniazid Inactivation: S. Sunahara, M. Urano, M. Ogawa	1530
	Preference for Clear versus Distorted Viewing in the Chimpanzee:  E. W. Menzel, Jr., and R. K. Davenport, Jr.	1531
	Influence of Cage Type and Dietary Zinc Oxide upon Molybdenum Toxicity:  G. L. Brinkman and R. F. Miller	1531
Association Affairs	128th Annual Meeting; Program Summary	1533
Departments	Forthcoming Events; New Products	1530
Departments *	Letters from R. Strauz-Hupé; H. E. Himwich and E. F. Rogers; N. Macdonald, F. Ward, N. H. Fletcher; D. K. Myers; S. K. Krishnaswami; W. Landauer,	
	R. H. Adamson, V. Paschkis: P. J. Kramer and J. V. Basmaiian	1559

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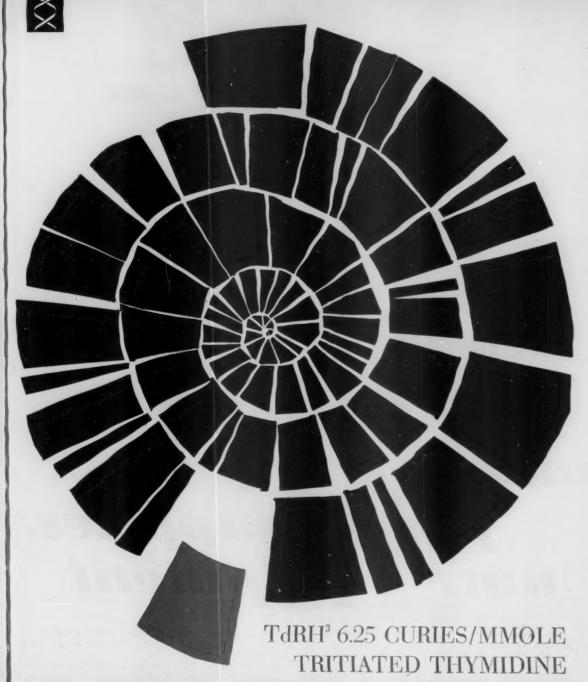
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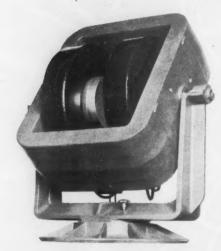
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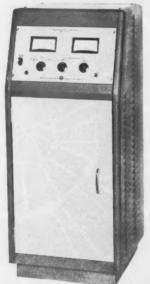


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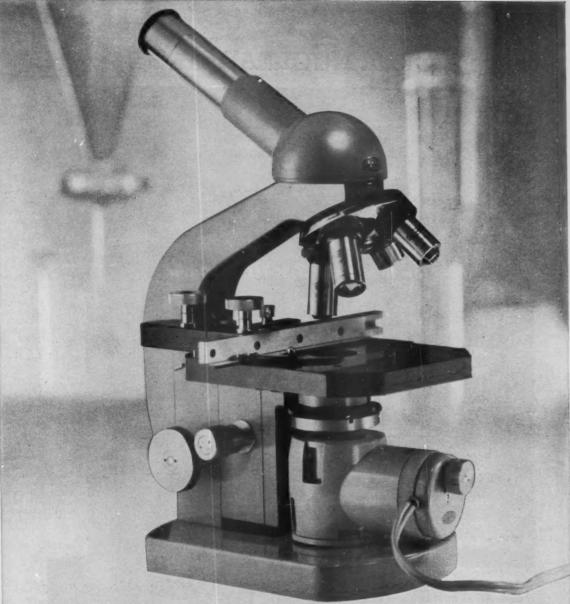
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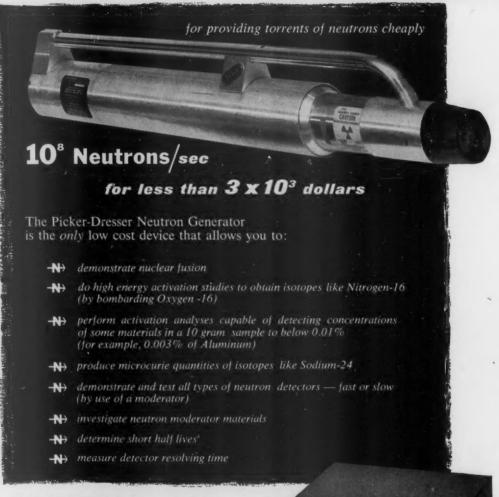
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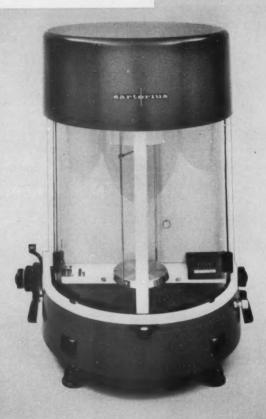
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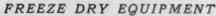
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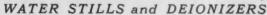
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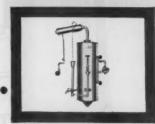
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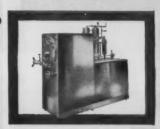


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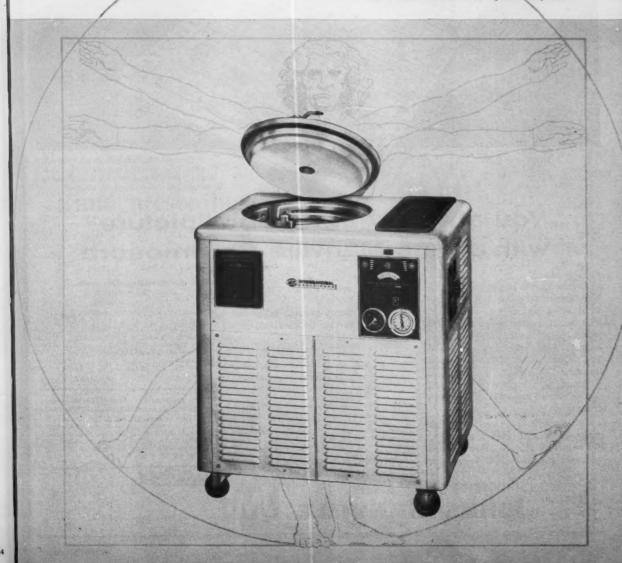
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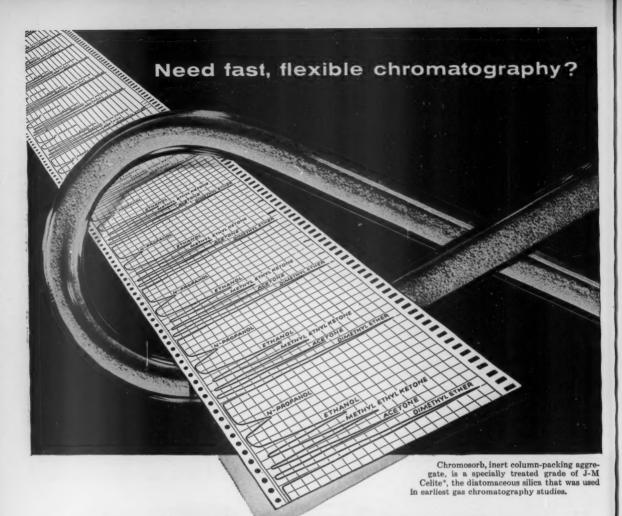
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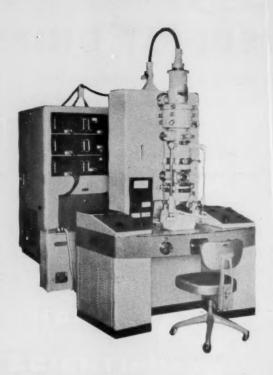
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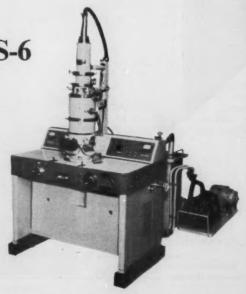
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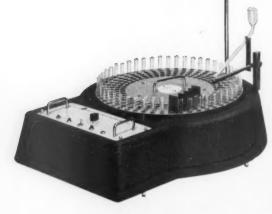
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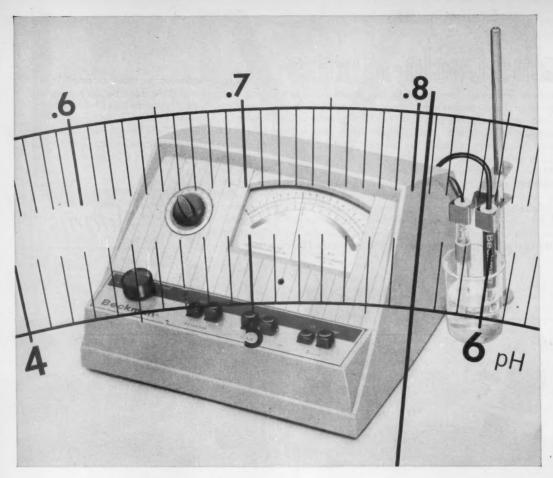


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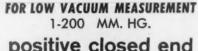


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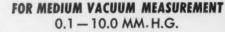
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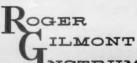
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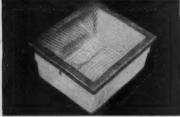
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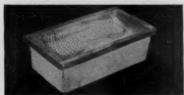
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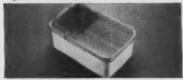
Number 40 Series cages can be used interchangeably for Hamsters and/or rats. #43 is made of clear Acrilonitrile-Styrene-Copolymer, #44 of Linear Polyethylene and #45 of translucent Polypropylene. All 40 Series lids are standard

 $\frac{1}{2}$ " mesh designed for rat housing and fit interchangeably on all 40 Series cages. All 30 Series lids also fit all 40 Series cages but have the  $\frac{5}{16}$ " for mice.



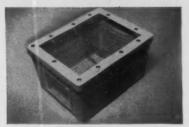
#### **ECONO-CAGE #30 SERIES**

Number 30 Series cages are designed as breeding and holding cages for mice. The over-all dimensions are 19" X 10½" X 5½" deep. Cage #32 is made of fiberglass, reinforced by plastic, Cage #33 is made of clear Acrylonitrile-Styrene Copolymer. Cage #34 is made of linear high density Polyethylene. Cage #35 is made of Polypropylene. All 30 Series lids are interchangeable on 30 Series cages.



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Over-all dimensions of the Econo-Cage general purpose unit are  $11\frac{1}{2}$ " X 8" X 6" deep. This cage is designed especially for laboratories with changing animal use requirements. It can be used to house mice, Hamsters, rats and guinea pigs. Because of its versatility, it is ideal in teaching situations. The cage is available with or without windows. It is made of fiberglass reinforced polyester plastic. All #12 lids can be used on General Purpose Cage #12.



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The small Restraining Cage #88 can be varied from 2" to 3½" in length and is 1¼" wide. Econo-Cage #90 can be varied from 4½" to 6" in length and is 2½" wide. Econo-Cage #91 can be varied from 5" to 7" in length and is 3" wide. All these units can be cleaned chemically or with hot water. They are not autoclavable.

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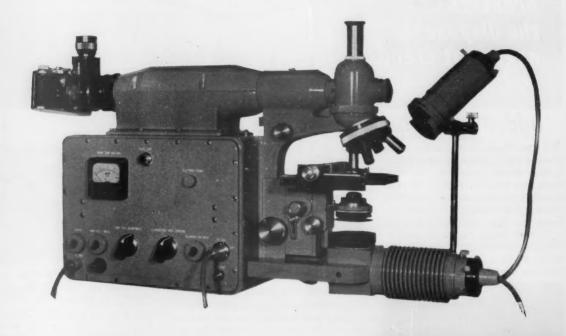


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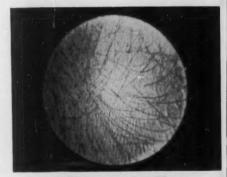
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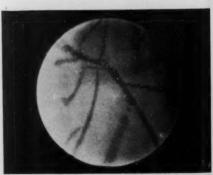
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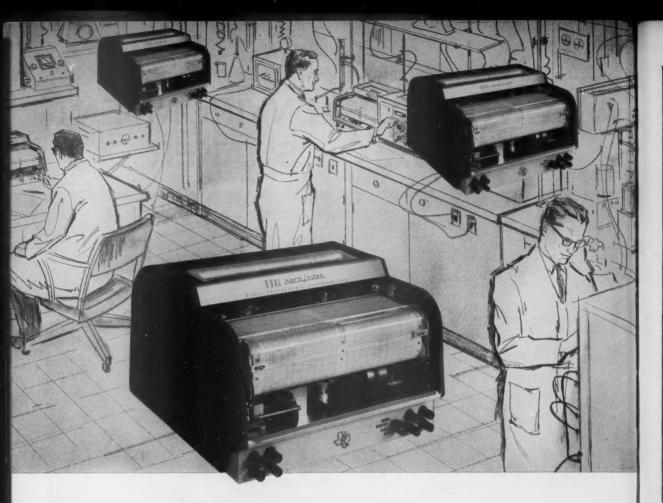
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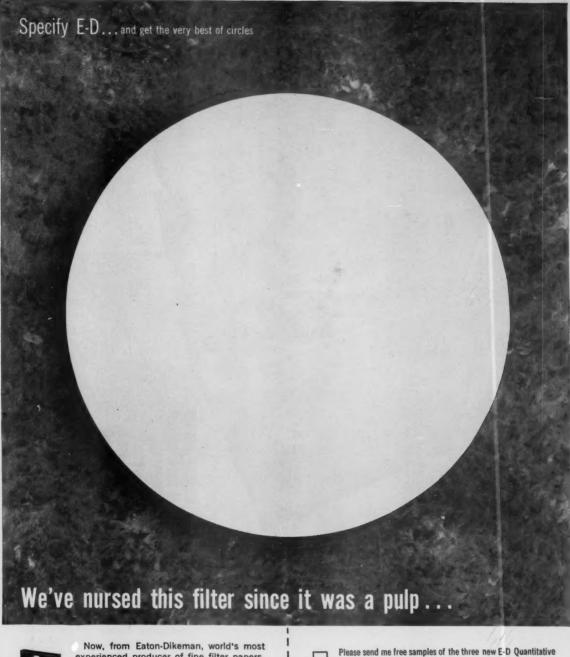
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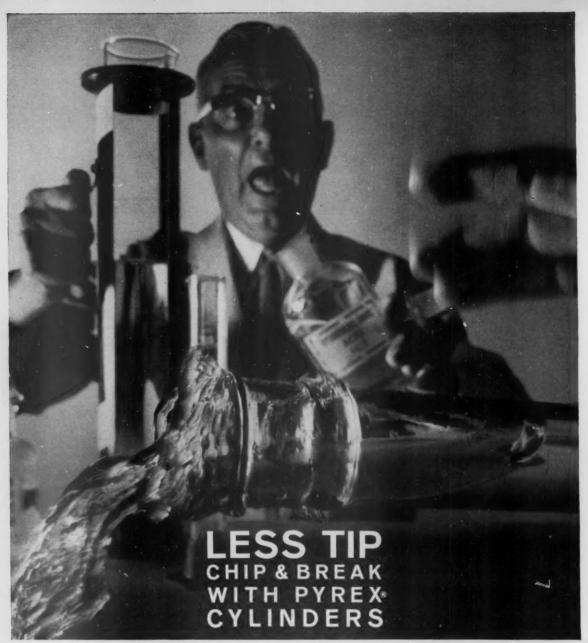
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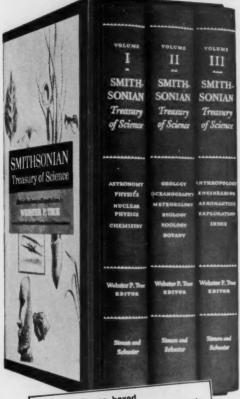
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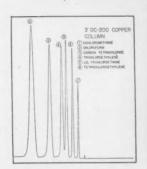
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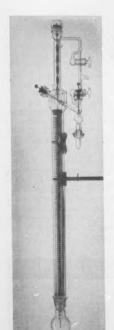
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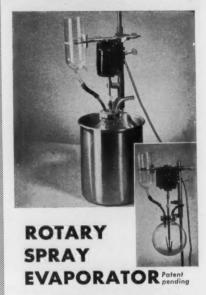
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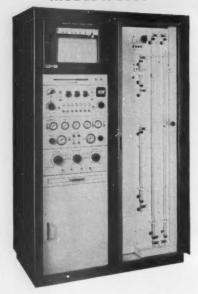
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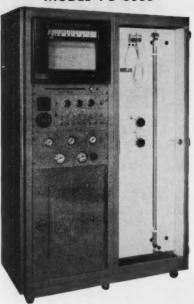


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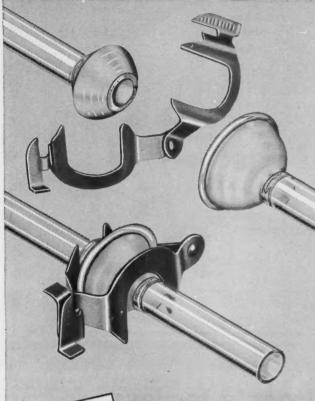
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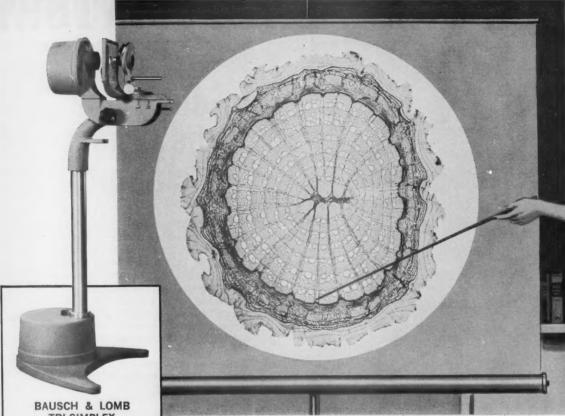
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"Say It Ain't So!"

What does a lexicographer owe to the language? The critics of Webster's Third New International Dictionary (1961) think that a dictionary ought to make it possible for its readers to distinguish good usage from bad and that it ought to maintain useful differentiations in meaning. To some extent the editors of the new edition disagree. The status label "colloquial" has been dropped. The nonsense formation irregardless was called erroneous or humorous in the 1958 printing of the second edition, but is called nonstandard in 1961. The much criticized ain't was stigmatized as dialect and illiterate in 1958; in 1961, although it was "disapproved by many," it was said to be "used orally in most parts of the U.S. by many cultivated speakers." This we doubt. Common speech blurs some distinctions. Common speech has come to use infer to mean imply, a change reflected in the dictionary without the notation that careful writers do not make this mistake.

So much for ordinary usage. The lexicographer may not pick and choose among scientific words even though he might wish to do so. Bad formations such as *Pleistocene* and *speedometer* are with us to stay and furnish bad examples for analogous coinages. If *speedometer* had been *speed-meter* it would have been English and we might have been spared *ceilometer*, which could have been *cloud-* or *sky-meter*.

But this is by the way. A sample list of 125 new scientific words and popular words generated by science was matched against the dictionary. Of the words (not all of them appear below) that first appeared in the Addenda of the 1958 printing, almost all achieved full status in 1961. Among them are: afterburner, antibiotics (as drugs), astronautics (but astronaut was not listed), analogue computer, binding energy, blue print (as a verb), brain washing, chromatography, fission and fusion (both in the nuclear sense), health physics, hybrid corn, narcoanalysis, nuclear reactor, operations research, pip (radar), radioisotope, radiation sickness, radome, tsunami, and servomechanism.

Among the slow bloomers—words that achieved full status only after lingering in the Addenda from 1945 on—are: actinomycin, ballistocardiograph, dendrochronology, fluorescent lamp, Geiger counter, gal, gramicidin, mass number, microwave, neutrino, and radar.

To find the words that appear for the first time in the 1961 edition is more difficult. Here are a few: antimatter, astronaut, astronavigation, blastoff, digital computer, fallout, free radical, gibberellic acid, information theory, imprinting (psychology), pad (in the senses of both "launching pad" and "residence"), radiocarbon, radio star, satellite (man-made), sputnik, strontium 90, and torr (for mm-Hg).

It is even more difficult to turn up words that are not listed. Most are of recent coinage or have only recently been used in a new sense. Some are: avoidance behavior, bionics, coesite, communications satellite, cosmonaut, optical maser or laser (maser, however, does appear), Mössbauer effect, reinforcement (psychology), systems approach, telegenesis (biology), and test ban.

The editor has paid his debt to science more fully than to general culture. His working rule that accuracy "requires a dictionary to state meanings in terms in which words are in fact used, not to give editorial opinion on what their meanings are" does better for technical terms than for English in general. We hope the next edition will distinguish more sharply and with more discrimination between illiterate and literate usage, both in speech and in writing.—G.DuS.



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## SCIENCE

## Pathways of Intracellular Hydrogen Transport

Absence of enzymatic hydrogen-carrying systems is a factor in aerobic glycolysis of malignant tissue.

George E. Boxer and Thomas M. Devlin

The formation of lactic acid from carbohydrate sources in the presence of an ample supply of oxygen-that is, aerobic glycolysis-is one of the most general and distinctive metabolic features of malignant tissues (1). The various hypotheses proposed to explain the imbalances between glycolysis and respiration in malignant tissues have been critically reviewed by Kit and Griffin (2) and concern four aspects of carbohydrate metabolism; (i) the concentration and activity of the glycolytic enzymes; (ii) deficiencies in the mitochondrial electron transport chain: (iii) relative inability of the mitochondria to oxidize pyruvate by way of the citric acid cycle; and (iv) failure of the normal regulatory mechanisms that control glycolysis and respiration. There are, undoubtedly, differences between many normal and malignant tissues in these areas, but the following summarizing statement of Kit and Griffin is still correct: "Although the detailed mechanism of the cancer [metabolic] imbalance remains unknown, its reality is not questioned. In particular, the imbalance between respiration and glycolysis first emphasized by Warburg [1] remains the foundation stone of biochemical investigation in cancer."

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The basic question is still unanswered: Why do most malignant tissues aerobically form appreciable quantities of lactate while most normal tissues do not? Both types of tissues qualitatively have the enzymatic equipment (lactic dehydrogenase) for the reduction of pyruvate to lactate, as well as the capability to metabolize pyruvate by way of the citric acid cycle.

This article (3) summarizes experimental data that support the suggestion of Weinhouse (4): "The extent to which pyruvic acid, a common intermediary in both respiration and glycolysis, competes for electrons held by the pyridine nucleotides with those factors that transport electrons to oxygen—namely, the flavoproteins and cytochromes—should be a crucial factor in determining the degree of aerobic glycolysis."

## Diphosphopyridine Nucleotide in Glycolysis

A condensed version of the glycolytic pathway from glucose to pyruvate is presented in Fig. 1. Two aspects of glycolysis need to be emphasized.

1) Evidence both from cell-fractionation studies (5, 6) and from studies of intact cells (7, 8) support the generally accepted concept that the enzymes and cofactors involved in glycolysis are primarily located in the cell sap—that is, the soluble extramitochondrial portion of the cytoplasm—of mammalian cells. The implications of this separation of

glycolysis from the terminal oxidative reactions of carbohydrate metabolism which occur in the mitochondria have been discussed by Lynen (7) and by Chance and Hess (8), as well as by others, and these authors have stressed the permeability barrier of the mitochondria as a major regulatory factor in cell metabolism.

Several investigators have reported that isolated mitochondria, primarily from brain (9, 10) and from mouse melanoma (11, 12), catalyze glycolysis. In most cases, however, only a small fraction of the total glycolytic activity remains with the mitochondria, even after a single washing (9, 11). These results indicate that the enzymes and cofactors are either loosely bound or are contaminants of the mitochondria (see 13). Irrespective of whether the enzymes (or perhaps only a few of the enzymes) are associated with the mitochondria or are strictly soluble in the cytoplasm of the intact cell, the evidence demonstrates (8) that the enzymes of glycolysis function with soluble extramitochondrial cofactors, particularly the coenzymes and adenine nucleotides.

2) In the glycolytic chain, a single oxidative reaction occurs—the oxidation of glyceraldehyde-3-phosphate to 1,3diphosphoglyceric acid. Diphosphopyridine nucleotide (DPN) is the obligatory acceptor of electrons in this reaction. Since DPN is present in only catalytic amounts in both normal and malignant mammalian cells (14), the presence of efficient mechanisms for the continuous oxidation of the reduced DPN (DPNH) generated is essential for the continued flow of carbon through this step and thus for the maintenance of glycolysis. The reduction of pyruvate to lactic acid by DPNH is one such mechanism, but the normal cell apparently must have other systems available which effectively compete with the lactic dehydrogenase reaction. Such systems in normal tissues, capable of competing with lactic dehydrogenase for the oxidation of extramitochondrial DPNH, are described later

The authors are affiliated with the Merck Institute for Therapeutic Research, Rahway, N.J. in this article, and the lack of these systems in malignant tissues is shown to favor the accumulation of lactic acid.

It should be emphasized, however, that the route of reoxidation of DPNH does not necessarily regulate glucose utilization in either normal or malignant tissues, since the activity of specific enzymes (for example, hexokinase) or the availability of phosphate (6) or adenosine di- and triphosphate (8) may control the rate of glycolysis.

#### Oxidation of DPNH by Mitochondria

Molecular oxygen is the ultimate acceptor of reducing equivalents from the oxidation of metabolic intermediates. The terminal transfer of reducing equivalents from substrates to oxygen is carried out within the mitochondria by various dehydrogenases (some of which are DPN-linked) in conjunction with the electron transport system. Mitochondrial oxidation of DPNH formed in the cell sap appears to be the most direct route for the transfer of reducing equivalents from the cell sap to oxygen. Lehninger (15), however, demonstrated that carefully isolated "intact" rat liver mitochondria do not oxidize added DPNH, and thus, extramitochondrial DPNH is presumably not a substrate for oxidation by way of the electron transport system. The inability to oxidize externally added DPNH is attributable to the impermeability of the mitochondrial membrane to this substrate, and is, in fact, a most sensitive criterion for the "intactness" of isolated liver mitochondria. Alteration of the mitochondrial membrane due to the isolation procedure, osmotic imbalances (15, 16), uncoupling agents, ageing, and chemical (17, 18) or mechanical (19) damage permits oxidation of external DPNH by mitochondria.

The observations of Lehninger with mitochondria from rat liver have been confirmed by other investigators (16) but have not been extended to mitochondrial preparations from many other tissues (18, 20). The results of a survey of the ability of isolated mitochondria from various tissues to oxidize externally added DPNH are presented in Table 1 (21). The values presented for oxygen uptake were determined polarographically with a microplatinum electrode. and with mitochondrial concentrations that manifested a high rate of oxygen uptake with succinate as substrate. Similar results were observed spectro-

photometrically by measuring the oxidation of DPNH at 340 millimicrons (21). With untreated mitochondria from normal and malignant tissues the rate of oxygen uptake was small, in many instances zero. When the mitochondrial structure was altered by pretreatment in a hypotonic medium, the rate of oxidation of DPNH was greatly increased, demonstrating that the respiratory mechanisms of these mitochondrial preparations were unimpaired.

Since all preparations, whether from normal or from malignant tissues, manifested a greater rate of DPNH oxidation after treatment in a hypotonic medium. it may be assumed that mitochondria from most tissues are impermeable to exogenous DPNH. The low rate of DPNH oxidation observed with most of the mitochondrial preparations before treatment indicates that only minimal damage to the mitochondria occurred during isolation. The relatively high rate of DPNH oxidation by "intact" heart mitochondria is probably a reflection of the lability of the mitochondrial membrane (22). Nevertheless, increased DPNH oxidation was observed after hypotonic treatment. Direct mitochondrial oxidation of external DPNH is, therefore, not available in most normal and malignant tissues, and the continual oxidation of DPNH necessary for maintenance of carbon flow through the glycolytic pathway must be catalyzed by other enzymatic systems.

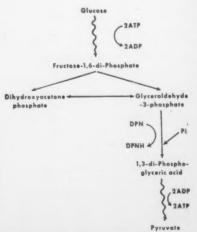


Fig. 1. A condensed version of the glycolytic pathway. *ADP*, adenosine diphosphate; *ATP*, adenosine triphosphate; *Pi*, inorganic phosphate; *DPN*, oxidized diphosphopyridine nucleotide; *DPNH*, reduced diphosphopyridine nucleotide.

#### Glycerophosphate "Shuttle"

Electrons can be carried from extramitochondrial DPNH to the intramitochondrial electron transport chain by indirect routes. In principle, any metabolite that can be reduced in the cell sap by DPNH to a product that is a substrate for mitochondrial oxidation can serve as a link in the transport of reducing equivalents across the mitochondrial membrane. To be effective, (i) such an acceptor must be formed continuously before or simultaneously with DPNH in carbohydrate metabolism, or (ii) the oxidized and reduced substrates must not be appreciably metabolized by the tissue, the compounds being thus permitted to function catalytically.

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A system of the first type is the socalled "glycerophosphate cycle" or, preferably, "shuttle," which has recently been studied in detail in both normal and malignant tissues (23-26). Dihydroxyacetonephosphate and glyceraldehyde-3phosphate are formed in equimolar amounts as the products of the action of aldolase on fructose-1,6-diphosphate. The very active triosephosphate isomerase establishes an equilibrium between these products which, by a ratio of 20 to 1, favors dihydroxyacetonephosphate, which can, in the presence of the soluble α-glycerophosphate dehydrogenase of the cell sap, accept electrons from DPNH to form L-α-glycerophosphate. Since DPNH is formed during the oxidation of glyceraldehydephosphate, the two enzymes, glyceraldehyde-3-phosphate and glycerophosphate dehydrogenase, form an effective dismutation system that leads to the continuous regeneration of DPN (27). Glycerophosphate also fulfills the second requirement for a system for intracellular hydrogen transport, since it is the substrate for an intramitochondrial enzyme that oxidizes glycerophosphate by way of the phosphorylating electron transport chain (28). Whereas the equilibrium of the soluble, DPN-linked glycerophosphate dehydrogenase greatly favors (by a ratio of 104 to 1) reduction of dihydroxyacetonephosphate, the equilibrium of the insoluble, intramitochondrial, flavin-linked glycerophosphate oxidase greatly favors oxidation of glycerophosphate. The alternate reduction of dihydroxyacetonephosphate and oxidation of glycerophosphate thus form an effective system for shuttling reducing equivalents from extramitochondrial DPNH to the intramitochondrial electron transport system.

In the metabolically very active musculature of a number of insects, the glycerophosphate "shuttle" provides a major route of hydrogen transport, particularly since these tissues have very low levels of lactic dehydrogenase, that can function as an extramitochondrial hydrogen-accepting system (23). The enzymatic equipment for this shuttle in normal mammalian tissues has been demonstrated for brain by Sacktor et al. (29), and for other tissues by Klingenberg and Slenczka (30). Ciaccio and Keller (26) demonstrated the dynamic functioning of this cycle with mitochondria isolated from the liver of hyperthyroid rats, which have exceptionally high glycerophosphate oxidase activity.

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A corollary of the function of glycerophosphate dehydrogenase in intracellular hydrogen transport is that glycerophosphate should accumulate, together with lactic acid, as an end product of anaerobic carbohydrate metabolism. This has been demonstrated by Ciaccio et al. (31) for homogenates of normal tissues and for the anaerobic glycolysis of normal tissues in situ. Even under aerobic conditions, glycerophosphate is found in considerable concentration in most normal tissues (32), since the mitochondrial oxidase has a relatively low substrate affinity  $(K_m \sim 1.0 \times 10^{-8} M)$ and effective oxidation of glycerophosphate does not occur below this concentration

#### Lack of Glycerophosphate "Shuttle" in Malignant Tissues

In most malignant tissues, glycerophosphate dehydrogenase activity, the component of this "shuttle" found in the cell sap, is either lacking or very low. Holzer et al. (33) first observed this lack in Ehrlich ascites and Yoshida hepatoma cells and stressed the significance of a change in the ratio of the two cytoplasmic hydrogen accepting systems, glycerophosphate dehydrogenase and lactic dehydrogenase. The ratios of activities of these enzymes (lactic to glycerophosphate dehydrogenase) in a variety of normal tissues of rodents (mice, rats, and hamsters), including regenerating liver and embryonic tissue, was found by Boxer and Shonk (25) to vary between 0.5 and 7.0 to 1, while this ratio ranged from 10:1 to several hundreds to 1 in a large series of tumors of rodents and human beings. The malignan-

cies studied included some 30 transplanted tumors, four human tumors growing in cortisonized hamsters, virusinduced malignancies of mice, and carcinogen-induced tumors of rats.

Similar changes were observed by Delbrück et al. (34) in other animal tumors, and by Sacktor and Dick (35) in a comparison of bone marrow and spleen with cells from myelogenic and lymphatic leukemias. In general, ascites forms of rodent tumors do not contain any measurable glycerophosphate dehydrogenase activity, and this suggests to possibility that the residual activity of solid tumors rests in the supporting stroma rather than in the malignant cell itself. Only histochemical localization of the enzyme can clarify this point,

The change in the ratio of lactic to glycerophosphate dehydrogenase was due, in each instance, to a drastically lowered activity in glycerophosphate dehydrogenase, although the imbalance was in some instances accentuated by a moderate increase in lactic dehydrogenase. The low glycerophosphate dehydrogenase activity, or complete lack of such activity, in malignant tissues is not due to the presence of any free inhibitor, since the addition of tumor extracts did not inhibit glycerophosphate dehydrogenase activity in normal tissues (25). The mitochondrial counterpart to the soluble dehydrogenase of the cell sap, the flavin-linked glycerophosphate oxidase, was found to be present in mitochondria from all malignant tissues tested. As compared to the activity of succinic oxidase, the activity of this enzyme was either normal or somewhat higher than in normal tissues (36).

Changes in enzymatic activities, even drastic ones, do not necessarily lead to changes in metabolic pattern, particularly if the individual enzyme activities are greatly in excess of the activity required to maintain the observed rate of metabolite flow, as is the case in glycolysis (6). Ciaccio et al. (31), however, demonstrated that there is also a drastic change in the end products of anaerobic glycolysis of tumors. Not only is glycerophosphate lacking in these tissues, but glycerophosphate is not produced by homogenates or by glycolysis in situ of malignant tissues. Furthermore, with homogenates of tumors, glycerophosphate formation can be restored by the addition of crystalline dehydrogenase to the level found in normal tissue.

Two exceptions to the pattern described should be noted: Essentially nor-

mal ratios of lactic to glycerophosphate dehydrogenase were observed in the ascitic Ehrlich-Lettré tumor of the mouse and the Morris hepatoma 5123 of the rat (37). While the Ehrlich carcinoma in the ascites form is free of any measurable glycerophosphate dehydrogenase activity, the Ehrlich-Lettré mutant of this ascites tumor has essentially "normal" activity of the enzyme. For reasons which are not as vet understood. the Ehrlich-Lettré tumor does not form glycerophosphate on glycolysis in vitro or in situ. The Morris hepatoma 5123 has low activity for both enzymes but in an essentially normal ratio, and on anaerobic glycolysis in vitro, this tissue does form glycerophosphate. This hepatoma is apparently an exceptional tumor, since Woods (38) has observed that the rate of anaerobic lactic acid formation. measured manometrically, is in the same range as in liver and not as high as in most tumors. But both the Ehrlich-Lettré and the Morris hepatoma 5123 tumors show a striking abnormality in another system for intracellular transfer of reducing equivalents.

## Acetoacetate- $\beta$ -Hydroxybutyrate "Shuttle"

Another pathway for the transfer of reducing equivalents from extramitochondrial DPNH to molecular oxygen, involving acetoacetate and β-hydroxybutyrate, has been described by Devlin and Bedell (39). In manometric experiments, the presence of catalytic quantities of acetoacetate increased, fourto sixfold, the oxidation of DPNH by freshly isolated "intact" mitochondria from rat liver. As shown in Fig. 2A, a stimulatory effect of acetoacetate has also been observed when oxygen uptake is measured polarographically with a platinum electrode. The presence of DPNH did not increase the respiration above that recorded for the endogenous rate. When acetoacetate was added, the low rate of oxygen uptake remained unchanged for several minutes, at which time the rate was increased four- to fivefold. The dashed curve of Fig. 2A is the respiration in the presence of DPNH if acetoacetate is not added. With a duplicate sample measured spectrophotometrically 340 millimicrons, the lack of oxidation of DPNH was confirmed. The addition of acetoacetate, however, initiated a rapid oxidation of DPNH, with no time delay, such as that observed in Fig. 2A for oxygen uptake. The lag observed in measurements of respiration is apparently due to the fact that only when enough  $\beta$ -hydroxybutyrate has accumulated to be oxidized by the mitochondria is there an increase in respiration.

Catalytic quantities of  $D(-)-\beta$ -hydroxybutyrate were as effective as acetoacetate in stimulating DPNH oxidation, whereas the L(+) isomer was inactive, demonstrating that the reaction was catalyzed by the  $D(-)-\beta$ -hydroxybutyrate dehydrogenase (40). There was a concomitant increase in phosphate uptake with the increase in respiration, yielding ratios of phosphate uptake to oxygen consumption in the range of 1.5:1 to 2.4:1.

A similar stimulatory effect by acetoacetate was observed in a system where DPNH was continuously generated by an alcohol dehydrogenase system. Other mitochondrial substrates (malate,  $\alpha$ -keto-glutarate, citrate, and so on) were without effect on DPNH oxidation (39), indicating that the increase in respiration observed when acetoacetate was added was not a nonspecific effect due to the presence of a substrate.

The interpretation that emerges is quite analogous to that given previously for the glycerophosphate "shuttle." Extramitochondrial DPNH reduces acetoacetate to D(-)- $\beta$ -hydroxybutyrate, which is then oxidized intramitochondrially to acetoacetate by an intramitochondrial dehydrogenase coupled to the phosphorylating electron transport chain. There is a difficulty with this interpretation in that  $\beta$ -hydroxybutyrate dehydrogenase is a tightly bound mito-

chondrial enzyme and there is no known soluble counterpart to the mitochondrial enzyme in the cell sap (41). The results become understandable, however, if the presence of β-hydroxybutyrate dehydrogenase activity in two locations in the mitochondrion is assumed: (i) at a locus that permits reaction with substrate and DPN external to the mitochondrion, and (ii) at a locus permitting interaction with the internal electron transport chain. The latter activity is the well-established intramitochondrial DPN-linked p(-)β-hydroxybutyrate dehydrogenase (41). The extramitochondrial activity of the dehydrogenase has also been demonstrated spectrophotometrically, as described above, where external DPNH did not react with the intramitochondrial electron transport system but was oxidized by acetoacetate. Studies of the stimulatory effect of added DPN and cytochrome c on \(\beta\)-hydroxybutyrate oxidation in the presence of the respiratory inhibitors Amytal and antimycin A also suggest the presence of two β-hydroxybutyrate dehydrogenase activities (40). Thus, the mitochondria apparently contain two different enzymes, spatially separated, reacting with the same substrate.

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In a recent report, Krebs et al. (42) have suggested that in liver the activity of the acetoacetate "shuttle" would be adequate for the oxidation of DPNH generated in the cell sap by the glyceraldehyde-3-phosphate dehydrogenase.

Oxidation of DPNH by mitochondria from ten transplanted and two induced rodent tumors was not stimulated by the addition of catalytic quantities of either acetoacetate or  $\beta$ -hydroxybutyrate (43). This is illustrated in Fig. 2B for mitochondria from the Morris hepatoma. As noted above, the Morris hepatoma 5123 does have the enzymatic capability to catalyze the  $\alpha$ -glycerophosphate "shuttle" but does not catalyze the acetoacetate pathway.

Whereas in the case of the glycerophosphate "shuttle" it was in all instances the cytoplasmic enzyme that was deleted in the neoplasm, the situation is more involved in the case of the acetoacetate "shuttle." Results indicate that either the "external" or the "internal" enzyme activity may be deleted, and that in some cases both activities are missing. The necessity for isolating fresh, well-preserved mitochondria, in sufficient quantity to permit detailed analysis of the enzyme deleted, makes the investigation of a large number of tumors difficult.

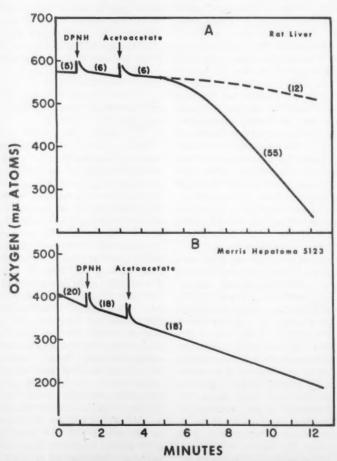


Fig. 2. Effect of acetoacetate on the oxidation of DPNH by mitochondria from rat liver and Morris hepatoma 5123. The incubation medium (1.5 ml), including KCl (0.10 M), as in Table 1. Oxygen uptake was measured polarographically. At the times indicated, DPNH (0.5  $\mu$ mole) and acetoacetate (1.5  $\mu$ mole) were added. The figures in parentheses represent oxygen uptake in millimicroatoms per minute.

#### Other Pathways

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The existence of other pathways to molecular oxygen for the oxidation of DPNH formed in the cell sap cannot be ruled out. As mentioned previously, any substance that can be reduced extramitochondrially by a pyridine-nucleotide-linked reaction and yields a product that is a substrate for mitochondrial oxidation can serve to transfer reducing equivalents. The potential importance of enzyme systems acting on the same substrates in the cell sap and the mitochondria has been stressed by Delbrück et al. (44), who proposed the term enzymes of type III for these systems. Among these, the malic and glutamic dehydrogenase systems are of particular interest as possible pathways. Both of these systems have been tested in normal tissues with the methodology described, but neither one functions as an intracellular hydrogen transport system.

Conover and Ernster (45) have proposed that the cytoplasmic nonspecific pyridine nucleotide diaphorase may serve in this capacity, the electron transfer being mediated by a quinone (vitamin K<sub>3</sub> or coenzyme Q). In a preliminary communication they reported that the oxidation by mitochemical of exogenous

Table 1. Oxidation of DPNH by isolated mitochondria from various tissues. The incubation medium (1.5 ml) contained phosphate buffer (pH, 7.4; 10 mM); Tris buffer (pH, 7.4; 10 mM); MgCl<sub>2</sub> (6.9 mM); adenosine diphosphate (0.3 mM); and DPNH (1 µmole). With untreated mitochondria, KCl (0.10 M) was also added. Oxygen uptake was measured polarographically with a platinum electrode (temperature, 24°C). Untreated mitochondria were isolated and suspended in 0.25 M sucrose or 2.5-percent polyvinylpyrrolidone-0.25 M sucrose and used immediately. In experiments with hypotonically treated mitochondria, the preparation was suspended in water and allowed to stand for 20 to 30 minutes at 24°C.

	Oxygen uptake (µato	om/hr per milligram of N)
Tissue	Untreated mitochondria	Hypotonic treatment of mitochondria
Liver, rat	0	7.4
Kidney, rat	1.2	14.4
Heart, rat	11.6	39.0
Novikoff hepatoma, rat	0.6	8.0
Dunning hepatoma, rat	0	7.9
Morris hepatoma 5123, rat	0	5.6
Crabb sarcoma, hamster	0	4.0
Walker carcinosarcoma 256, rat	0.8	2.5
Mammary tumor, rat (3-methylcholanthrene-induced)	0.1	5.6
Ehrlich-Lettré ascites, mouse	0.4	9.2
Novikoff ascites, rat	0.8	10.1

DPNH and reduced triphosphopyridine nucleotide is stimulated by the addition of purified diaphorase and vitamin Ks. The relationship of this system to the well-established stimulation of DPNH oxidation by cytochrome c and the extramitochondrial cytochrome c reductase has yet to be established. Kaplan et al. (46), have suggested that a specific DPN-DPN transhydrogenase may serve

to link extramitochondrial DPNH with the intramitochondrial electron transport system. Stein et al. (47), however, have reported that the activity of the DPN-DPN transhydrogenase is increased by digitonin treatment of the mitochondria, a finding which indicates that the enzyme may be located within the mitochondrion and have a specific function intramitochondrially, as previ-

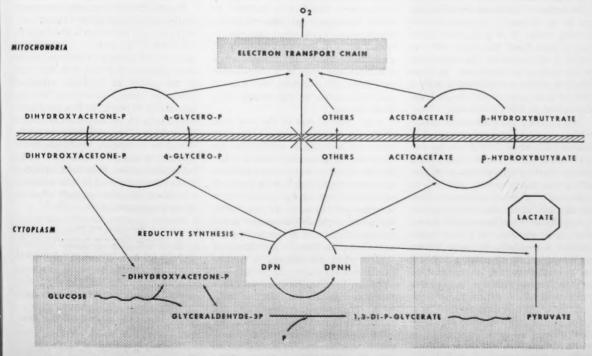


Fig. 3. Pathways of intracellular hydrogen transport.

ously proposed (46, 48). In addition, the results in Table 1 also exclude the proposed extramitochondrial link.

Other intracellular hydrogen transport systems can be theoretically constructed from known enzymatic oxidation-reduction reactions and are under active investigation.

#### Oxidation of Cytoplasmic DPNH

In Fig. 3 are summarized the various pathways which are potentially available for the oxidation in normal tissues of DPNH in the cell sap, Figure 3 emphasizes the compartmentalization of various phases of carbohydrate metabolism within the cell, and the importance of intracellular hydrogen transport systems in regulation of aerobic lactic acid formation. The central role of DPN in the maintenance of the flow of carbon through the glycolytic path and the known transmission belts of electrons from the oxidation of glyceraldehyde-3phosphate to the phosphorylating electron transport chain inside the mitochondria are indicated. The lack of direct reaction of DPNH with the mitochondrial oxidation system in either normal or malignant tissues is denoted by the intercepted direct (vertical) arrow.

It should be emphasized that the relative importance of any one of the pathways presented in the electron flow has yet to be determined for each specific normal tissue. It is quite conceivable that a given tissue may have only one pathway of importance, the other being of low activity or nonexistent. An absolute determination of the contribution of each of these systems will require techniques not available at this time.

Irrespective of the existence of "other" pathways, at least three routes by which extramitochondrial DPNH can be oxidized are available to cells from normal tissues: (i) the glycerophosphate system, (ii) the acetoacetate system, and (iii) the reduction of pyruvate to lactate. Since at least two of the three pathways are not available to malignant cells, the reduction of pyruvate to lactate would become a metabolic necessity for the malignant cell in resupplying DPN for steady-state glycolysis. Under anaerobiosis the first two pathways are cut off in the normal cell, and it too forms lactic acid, but on recovery, the reoxidation of lactic acid is possible, since mitochondrial systems are open for regeneration of DPN.

The reduction of pyruvate to lactate

is not the only cytoplasmic anaerobic system that can utilize DPNH. A number of reactions in fat, amino acid, and nucleotide synthesis require reducing equivalents. It is of considerable interest that the malignant cell is poised in a metabolic equilibrium that is favorable to reductive synthesis and that could, therefore, provide the metabolic climate for one of the most striking pathological features of the malignant cell-the potential for growth. Many of the synthetic reductive reactions are, however, TPNlinked rather than DPN-linked, An effective DPN-TPN transhydrogenase enzyme has been described by Kaplan et al. (46), but it is an intramitochondrial enzyme and, furthermore, has been reported to be deleted in at least one tumor (49). The effectiveness of the steroidcoupled transhydrogenase systems that have been described by Talalay and Williams-Ashman (50), as well as by others, remain to be investigated in malignant tissues.

#### Consequence of Altered Pathway

The failure of malignant tissues to oxidize DPNH by way of one of the described "shuttles" to the phosphorylating electron transport chain entails the loss of at least two high-energy phosphate bonds available from the glycolytic system. This loss is, however, of minor importance as compared to the energy potential lost when pyruvate becomes an obligatory electron acceptor, since each mole of lactic acid formed withdraws one mole of a three-carbon unit from end oxidation, and thus 15 mole equivalents of high-energy phosphate are lost.

Lactic acid is one of the rare dead ends in a mammalian metabolic path, since it is not directly oxidized by the mitochondria, is not aminated or decarboxylated, and the only way for the three carbons to return to the main stream of metabolic events is by reoxidation to pyruvic acid by way of the DPN-dependent lactic dehydrogenase in the cell sap. This route, of course, requires systems for the effective reoxidation of DPNH which are limiting in the malignant cell,

As noted earlier, there is no indication that the enzymes of the citric acid cycle, or the condensing enzyme in particular, are lacking in tumors (51), although the number of mitochondria per cell is usually smaller than in normal tissues (2). In spite of the presence of the

enzymes required for oxidation of pyruvate, Busch (52) observed that injected labeled pyruvate (2-C14) was primarily converted to lactic acid by tumor tissue, in contrast to findings in a number of normal tissues. In experiments with tissue slices, the percentage of added pyruvate that was converted to lactate increased in the presence of added glucose in tumors but not in normal tissues (53). This again would be the expected result if increased flow through the glycolytic path requires increased oxidation of DPNH, for such oxidation can be achieved in normal tissues by way of aerobic pathways, but in the malignant tissue it has to be accomplished primarily by reduction of pyruvate to lactate.

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Inhibition of lactic dehydrogenase formation has been proposed in cancer chemotherapy, primarily on the basis that lactic acid formation is a characteristic feature of malignant cells (54). The reduction of pyruvate to lactate is, however, a metabolic necessity for the malignant cell, as indicated by the data here summarized, whereas in the normal cell it is only one of at least three pathways available under aerobic conditions (Fig. 3). It would seem to be a reasonable working hypothesis that effective inhibition of lactic dehydrogenase would embarrass the normal cell only to a limited degree but would have major metabolic consequences in malignant cells.

Finally, the data presented have some bearing on the question of whether aerobic lactic acid formation is the cause or the effect of the malignant transformation. It is the deletion of enzymes, in the sense proposed by Potter (55), that leads to the failure of hydrogen transport within the internal structure of the malignant cell. If, therefore, it is the genetic information for the formation or control of synthesis of some of the enzymes involved in intracellular hydrogen transport that is deleted or altered, it would follow that aerobic lactic acid formation is the effect of a change-for whatever reason-in the chromosomal structure of the malignant cell.

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## Cause and Effect in Biology

Kinds of causes, predictability, and teleology are viewed by a practicing biologist.

Ernst Mayr

Being a practicing biologist I feel that I cannot attempt the kind of analysis of cause and effect in biological phenomena that a logician would undertake. I would instead like to concentrate on the special difficulties presented by the classical concept of causality in biology. From the first attempts to achieve a unitary concept of cause, the student of causality has been bedeviled by these difficulties. Descartes's grossly mechanistic interpretation of life, and the logical extreme to which his ideas were carried by Holbach and de la Mettrie, inevitably provoked a reaction leading to vitalistic theories which have been in vogue, off and on, to the present day. I have only to mention names like Driesch (entelechy), Bergson (élan vital), and Lecomte du Noüv, among the more prominent authors of the recent past. Though these authors may differ in particulars, they all agree in claiming that living beings and life processes cannot be causally explained in terms of physical and chemical phenomena. It is our task to ask whether this assertion is justified, and if we answer this question with "no," to determine the source of the misunderstanding.

Causality, no matter how it is defined in terms of logic, is believed to contain three elements: (i) an explanation of past events ("a posteriori causality"); (ii) prediction of future events; and (iii) interpretation of teleological-that is, "goal-directed"-phenomena.

The three aspects of causality (ex-

planation, prediction, and teleology) must be the cardinal points in any discussion of causality and were quite rightly singled out as such by Nagel (1). Biology can make a significant contribution to all three of them. But before I can discuss this contribution in detail, I must say a few words about biology as a science.

#### Biology

The word biology suggests a uniform and unified science. Yet recent developments have made it increasingly clear that biology is a most complex areaindeed, that the word biology is a label for two largely separate fields which differ greatly in method, Fragestellung, and basic concepts. As soon as one goes beyond the level of purely descriptive structural biology, one finds two very different areas, which may be designated functional biology and evolutionary biology. To be sure, the two fields have many points of contact and overlap. Any biologist working in one of these fields must have a knowledge and appreciation of the other field if he wants

The author is Alexander Agassiz professor of cology at Harvard University and director of the Museum of Comparative Zoology, Harvard College, Cambridge, Mass. This article is adapted from a lecture presented 1 February 1961 at Massachusetts Institute of Technology in the 1960-61 series of Hayden lectures on "Cause and Effect". to avoid the label of a narrow-minded specialist. Yet in his own research he will be occupied with problems of either one or the other field. We cannot discuss cause and effect in biology without first having characterized these two fields.

Functional biology. The functional biologist is vitally concerned with the operation and interaction of structural elements, from molecules up to organs and whole individuals. His ever-repeated question is "How?" How does something operate, how does it function? The functional anatomist who studies an articulation shares this method and approach with the molecular biologist who studies the function of a DNA molecule in the transfer of genetic information. The functional biologist attempts to isolate the particular component he studies, and in any given study he usually deals with a single individual, a single organ, a single cell, or a single part of a cell. He attempts to eliminate, or control, all variables, and he repeats his experiments under constant or varying conditions until he believes he has clarified the function of the element he studies. The chief technique of the functional biologist is the experiment, and his approach is essentially the same as that of the physicist and the chemist. Indeed, by isolating the studied phenomenon sufficiently from the complexities of the organism, he may achieve the ideal of a purely physical or chemical experiment. In spite of certain limitations of this method, one must agree with the functional biologist that such a simplified approach is an absolute necessity for achieving his particular objectives. The spectacular success of biochemical and biophysical research justifies this direct, although distinctly simplistic, approach.

Evolutionary biology. The evolutionary biologist differs in his method and in the problems in which he is interested. His basic question is "Why?" When we say "why" we must always be aware of the ambiguity of this term. It may mean "how come?," but it may also mean the finalistic "what for?" It is obvious that the evolutionist has in mind the historical "how come?" when he asks "why?" Every organism, whether individual or species, is the product of a long history, a history which indeed dates back more than 2000 million years. As Max Delbrück (2) has said, "a mature physicist, acquainting himself for the first time with the problems of biology, is puzzled by the circumstance that there are no 'absolute

phenomena' in biology. Everything is time-bound and space-bound. The animal or plant or micro-organism he is working with is but a link in an evolutionary chain of changing forms, none of which has any permanent validity." There is hardly any structure or function in an organism that can be fully understood unless it is studied against this historical background. To find the causes for the existing characteristics, and particularly adaptations, of organisms is the main preoccupation of the evolutionary biologist. He is impressed by the enormous diversity of the organic world. He wants to know the reasons for this diversity as well as the pathway by which it has been achieved. He studies the forces that bring about changes in faunas and floras (as in part documented by paleontology), and he studies the steps by which have evolved the miraculous adaptations so characteristic of every aspect of the organic world.

We can use the language of information theory to attempt still another characterization of these two fields of biology. The functional biologist deals with all aspects of the decoding of the programmed information contained in the DNA code of the fertilized zygote. The evolutionary biologist, on the other hand, is interested in the history of these codes of information and in the laws that control the changes of these codes from generation to generation. In other words, he is interested in the causes of these changes.

Many of the old arguments of biological philosophy can be stated far more precisely in terms of these genetic codes. For instance, as Schmalhausen, in Russia, and I have pointed out independently, the inheritance of acquired characteristics becomes quite unthinkable when applied to the model of the transfer of genetic information from a peripheral phenotype to the DNA of the germ cells.

But let us not have an erroneous concept of these codes. It is characteristic of these genetic codes that the programming is only in part rigid. Such phenomena as learning, memory, nongenetic structural modification, and regeneration show how "open" these programs are. Yet, even here there is great specificity, for instance with respect to what can be "learned," at what stage in the life cycle "learning" takes place, and how long a memory engram is retained. The program, then, may be in part quite unspecific, and yet the range of possible variation is itself included in

the specifications of the code. The codes, therefore, are in some respects highly specific; in other respects they merely specify "reaction norms" or general capacities and potentialities.

Let me illustrate this duality of codes by the difference between two kinds of birds with respect to "species recognition." The young cowbird is raised by foster parents-let us say, in the nest of a song sparrow or warbler. As soon as it becomes independent of its foster parents it seeks the company of other young cowbirds, even though it has never seen a cowbird before! In contrast, after hatching from the egg, a young goose will accept as its parent the first moving (and preferably also calling) object it can follow and become "imprinted" to. What is programmed is, in one case, a definite "gestalt," in the other, merely the capacity to become imprinted to a "gestalt." Similar differences in the specificity of the inherited program are universal throughout the organic world.

Let us now get back to our main topic and ask: Is cause the same thing in functional and evolutionary biology?

Max Delbrück, again, has reminded us (2) that as recently as 1870 Helmholtz postulated "that the behavior of living cells should be accountable in terms of motions of molecules acting under certain fixed force laws." Now, says Delbrück correctly, we cannot even account for the behavior of a single hydrogen atom. As he also says, "any living cell carries with it the experiences of a billion years of experimentation by its ancestors."

Let me illustrate the difficulties of the concept of causality in biology by an example. Let us ask: What is the cause of bird migration? Or more specifically: Why did the warbler on my summer place in New Hampshire start his southward migration on the night of the 25th of August?

I can list four equally legitimate causes for this migration.

1) An ecological cause. The warbler, being an insect eater, must migrate, because it would starve to death if it should try to winter in New Hampshire.

2) A genetic cause. The warbler has acquired a genetic constitution in the course of the evolutionary history of its species which induces it to respond appropriately to the proper stimuli from the environment. On the other hand, the screech owl, nesting right next to it, lacks this constitution and does not respond to these stimuli. As a result, it is sedentary.

. 3) An intrinsic physiological cause. The warbler flew south because its migration is tied in with photoperiodicity. It responds to the decrease in day length and is ready to migrate as soon as the number of hours of daylight have dropped below a certain level.

4) An extrinsic physiological cause. Finally, the warbler migrated on the 25th of August because a cold air mass, with northerly winds, passed over our area on that day. The sudden drop in temperature and the associated weather conditions affected the bird, already in a general physiological readiness for migration, so that it actually took off on that particular day.

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Now, if we look over the four causations of the migration of this bird once more we can readily see that there is an immediate set of causes of the migration, consisting of the physiological condition of the bird interacting with photoperiodicity and drop in temperature. We might call these the proximate causes of migration. The other two causes, the lack of food during winter and the genetic disposition of the bird, are the ultimate causes. These are causes that have a history and that have been incorporated into the system through many thousands of generations of natural selection. It is evident that the functional biologist would be concerned with analysis of the proximate causes, while the evolutionary biologist would be concerned with analysis of the ultimate causes. This is the case with almost any biological phenomenon we might want to study. There is always a proximate set of causes and an ultimate set of causes; both have to be explained and interpreted for a complete understanding of the given phenomenon.

Still another way to express these differences would be to say that proximate causes govern the responses of the individual (and his organs) to immediate factors of the environment while ultimate causes are responsible for the evolution of the particular DNA code of information with which every individual of every species is endowed. The logician will, presumably, be little concerned with these distinctions. Yet, the biologist knows that many heated arguments about the "cause" of a certain biological phenomenon could have been avoided if the two opponents had realized that one of them was concerned with proximate and the other with ultimate causes. I might illustrate this by a quotation from Loeb (3): "The earlier writers explained the growth of the legs in the tadpole of the frog or toad as a

case of adaptation to life on land. We know through Gudernatsch that the growth of the legs can be produced at any time even in the youngest tadpole, which is unable to live on land, by feeding the animal with the thyroid gland."

Let us now get back to the definition of "cause" in formal philosophy and see how it fits with the usual explanatory "cause" of functional and evolutionary biology. We might, for instance, define cause as "a nonsufficient condition without which an event would not have happened," or as "a member of a set of jointly sufficient reasons without which the event would not happen" [after Scriven (4)]. Definitions such as these describe causal relations quite adequately in certain branches of biology. particularly in those which deal with chemical and physical unit phenomena. In a strictly formal sense they are also applicable to more complex phenomena, and yet they seem to have little operational value in those branches of biology that deal with complex systems. I doubt that there is a scientist who would question the ultimate causality of all biological phenomena-that is, that a causal explanation can be given for past biological events. Yet such an explanation will often have to be so unspecific and so purely formal that its explanatory value can certainly be challenged. In dealing with a complex system, an explanation can hardly be considered very illuminating that states: "Phenomenon A is caused by a complex set of interacting factors, one of which is b." Yet often this is about all one can say. We will have to come back to this difficulty in connection with the problem of prediction. However, let us first consider the problem of teleology.

#### Teleology

No discussion of causality is complete which does not come to grips with the problem of teleology. This problem had its beginning with Aristotle's classification of causes, one of the categories being the "final" causes. This category is based on the observation of the orderly and purposive development of the individual from the egg to the "final" stage of the adult, and of the development of the whole world from its beginnings (chaos?) to its present order. Final cause has been defined as "the cause responsible for the orderly reaching of a preconceived ultimate goal." All goal-seeking behavior has been classified as "teleological," but so have

many other phenomena that are not necessarily goal-seeking in nature.

Aristotelian scholars have rightly emphasized that Aristotle-by training and interest-was first and foremost a biologist, and that it was his preoccupation with biological phenomena which dominated his ideas on causes and induced him to postulate final causes in addition to the material, formal, and efficient causes. Thinkers from Aristotle to the present have been challenged by the apparent contradiction between a mechanistic interpretation of natural processes and the seemingly purposive sequence of events in organic growth, in reproduction, and in animal behavior. Such a rational thinker as Bernard (5) has stated the paradox in these words.

There is, so to speak, a preestablished design of each being and of each organ of such a kind that each phenomenon by itself depends upon the general forces of nature, but when taken in connection with the others it seems directed by some invisible guide on the road it follows and led to the place it occupies.

We admit that the life phenomena are attached to physicochemical manifestations, but it is true that the essential is not explained thereby; for no fortuitous coming together of physicochemical phenomena constructs each organism after a plan and a fixed design (which are foreseen in advance) and arouses the admirable subordination and harmonious agreement of the acts of life. . . Determinism can never be [anything] but physicochemical determinism. The vital force and life belong to the metaphysical world.

What is the x, this seemingly purposive agent, this "vital force," in organic phenomena? It is only in our lifetime that explanations have been advanced which deal adequately with this paradox.

The many dualistic, finalistic, and vitalistic philosophies of the past merely replaced the unknown x by a different unknown, y or z, for calling an unknown factor entelechia or élan vital is not an explanation. I shall not waste time showing how wrong most of these past attempts were. Even though some of the underlying observations of these conceptual schemes are quite correct, the supernaturalistic conclusions drawn from these observations are altogether misleading.

Where, then, is it legitimate to speak of purpose and purposiveness in nature, and where is it not? To this question we can now give a firm and unambiguous answer. An individual who—to use the language of the computer—has been "programmed" can act purposefully. Historical processes, however, can not act purposefully. A bird that starts its migration, an insect that selects its

host plant, an animal that avoids a predator, a male that displays to a female—they all act purposefully because they have been programmed to do so. When I speak of the programmed "individual," I do so in a broad sense. A programmed computer itself is an "individual" in this sense, but so is, during reproduction, a pair of birds whose instinctive and learned actions and interactions obey, so to speak, a single program.

The completely individualistic and yet also species-specific DNA code of every zygote (fertilized egg cell), which controls the development of the central and peripheral nervous systems, of the sense organs, of the hormones, of physiology and morphology, is the *program* for the behavior computer of this individual.

Natural selection does its best to favor the production of codes guaranteeing behavior that increases fitness. A behavior program that guarantees instantaneous correct reaction to a potential food source, to a potential enemy, or to a potential mate will certainly give greater fitness in the Darwinian sense than a program that lacks these properties. Again, a behavior program that allows for appropriate learning and the improvement of behavior reactions by various types of feedbacks gives greater likelihood of survival than a program that lacks these properties.

The purposive action of an individual, insofar as it is based on the properties of its genetic code, therefore is no more nor less purposive than the actions of a computer that has been programmed to respond appropriately to various inputs. It is, if I may say so, a purely mechanistic purposiveness.

We biologists have long felt that it is ambiguous to designate such programmed, goal-directed behavior "teleological," because the word teleological has also been used in a very different sense, for the final stage in evolutionary adaptive processes. When Aristotle spoke of final causes he was particularly concerned with the marvelous adaptations found throughout the plant and animal kingdom. He was concerned with what later authors have called design or plan in nature. He ascribed to final causes not only mimicry or symbiosis but all the other adaptations of animals and plants to each other and to their physical environment. The Aristotelians and their successors asked themselves what goal-directed process could have produced such a well-ordered design in nature.

It is now evident that the terms teleology and teleological have been applied to two entirely different sets of phenomena. On one hand is the production and perfecting throughout the history of the animal and plant kingdoms of ever-new programs and of everimproved DNA codes of information. On the other hand there is the testing of these programs and the decoding of these codes throughout the lifetime of each individual. There is a fundamental difference between, on the one hand, end-directed behavioral activities or developmental processes of an individual or system, which are controlled by a program, and, on the other hand, the steady improvement of genetic codes. This genetic improvement is evolutionary adaptation controlled by natural selection.

In order to avoid confusion between the two entirely different types of end direction, Pittendrigh (6) has introduced the term teleonomic as a descriptive term for all end-directed systems "not committed to Aristotelian teleology." Not only does this negative definition place the entire burden on the word system, but it makes no clear distinction between the two teleologies of Aristotle. It would seem useful to restrict the term teleonomic rigidly to systems operating on the basis of a program, a code of information. Teleonomy in biology designates "the apparent purposefulness of organisms and their characteristics," as Julian Huxley expressed it (7).

Such a clear-cut separation of teleonomy, which has an analyzable physicochemical basis, from teleology, which deals more broadly with the over-all harmony of the organic world, is most useful because these two entirely different phenomena have so often been confused with each other.

The development or behavior of an individual is purposive, natural selection is definitely not. When MacLeod (8) stated, "What is most challenging about Darwin, however, is his re-introduction of purpose into the natural world," he chose the wrong word. The word purpose is singularly inapplicable to evolutionary change, which is, after all, what Darwin was considering. If an organism is well adapted, if it shows superior fitness, this is not due to any purpose of its ancestors or of an outside agency, such as "Nature" or "God," who created a superior design or plan. Darwin "has swept out such finalistic teleology by the front door," as Simpson (9) has rightly said.

We can summarize this discussion by stating that there is no conflict between causality and teleonomy, but that scientific biology has not found any evidence that would support teleology in the sense of various vitalistic or finalistic theories (9, 10). All the so-called teleological systems which Nagel discusses (11) are actually illustrations of teleonomy.

#### The Problem of Prediction

The third great problem of causality in biology is that of prediction. In the classical theory of causality the touchstone of the goodness of a causal explanation was its predictive value. This view is still maintained in Bunge's modern classic (12): "A theory can predict to the extent to which it can describe and explain." It is evident that Bunge is a physicist; no biologist would have made such a statement. The theory of natural selection can describe and explain phenomena with considerable precision, but it cannot make reliable predictions, except through such trivial and meaningless circular statements as, for instance: "the fitter individuals will on the average leave more offspring." Scriven (13) has emphasized quite correctly that one of the most important contributions to philosophy made by the evolutionary theory is that it has demonstrated the independence of explanation and prediction.

Although prediction is not an Inseparable concomitant of causality, every scientist is nevertheless happy if his causal explanations simultaneously have high predictive value. We, can distinguish many categories of prediction in biological explanation. Indeed, it is even doubtful how to define "prediction" in biology. A competent zoogeographer can predict with high accuracy what animals will be found on a previously unexplored mountain range or island. A paleontologist likewise can predict with high probability what kind of fossils can be expected in a newly accessible geological horizon. Is such correct guessing of the results of past events genuine prediction? A similar doubt pertains to taxonomic predictions, as discussed in the next paragraph. The term prediction is, however, surely legitimately used for future events. Let me give you four examples to illustrate the range of predictability.

1) Prediction in classification. If I have identified a fruit fly as an individual of Drosophila melanogaster on the basis of bristle pattern and the propor-

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tions of face and eye, I can "predict" numerous structural and behavioral characteristics which I will find if I study other aspects of this individual. If I find a new species with the diagnostic key characters of the genus *Drosophila*, I can at once "predict" a whole set of biological properties.

2) Prediction of most physicochemical phenomena on the molecular level. Predictions of very high accuracy can be made with respect to most biochemical unit processes in organisms, such as metabolic pathways, and with respect to biophysical phenomena in simple systems, such as the action of light, heat, and electricity in physiology.

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In examples 1 and 2 the predictive value of causal statements is usually very high. Yet there are numerous other generalizations or causal statements in biology that have low predictive values. The following examples are of this kind.

3) Prediction of the outcome of complex ecological interactions. The statement, "An abandoned pasture in southern New England will be replaced by a stand of grey birch (Betula populifolia) and white pine (Pinus strobus)" is often correct. Even more often, however, the replacement may be an almost solid stand of P. strobus, or P. strobus may be missing altogether and in its stead will be cherry (Prunus), red cedar (Juniperus virginianus), maples, sumac, and several other species.

Another example also illustrates this unpredictability. When two species of flour beetles (*Tribolium confusum* and *T. castaneum*) are brought together in a uniform environment (sifted wheat flour), one of the two species will always displace the other. At high temperatures and humidities, *T. castaneum* will win out; at low temperatures and humidities, *T. confusum* will be the victor. Under intermediate conditions the outcome is indeterminate and hence unpredictable (Table 1) (14).

4) Prediction of evolutionary events. Probably nothing in biology is less predictable than the future course of evolution. Looking at the Permian reptiles, who would have predicted that most of the more flourishing groups would become extinct (many rather rapidly), and that one of the most undistinguished branches would give rise to the mammals? Which student of the Cambrian fauna would have predicted the revolutionary changes in the marine life of the subsequent geological eras? Unpredictability also characterizes small-scale evolution. Breeders and students of natural selection have discovered again

Table 1. Two species of *Tribolium* in competition [from Park (14)].

Co	ndition	Replicas	Victorious specie (No. of trials)	
Temp.	Humidity (%)	(No.)	T. con- fusum	T. cast- aneum
34	70	30		30
29	70	66	11	55
24	70	30	21	9
34,29	30	60	53	7
24	30	20	20	

and again that independent parallel lines exposed to the same selection pressure will respond at different rates and with different correlated effects, none of them predictable.

As is true in many other branches of science, the validity of predictions for biological phenomena (except for a few chemical or physical unit processes) is nearly always statistical. We can predict with high accuracy that slightly more than 500 of the next 1000 newborns will be boys. We cannot predict the sex of a particular unborn child.

#### Reasons for Indeterminacy in Biology

Without claiming to exhaust all the possible reasons for indeterminacy, I can list four classes. Although they somewhat overlap each other, each deserves to be treated separately.

1) Randomness of an event with respect to the significance of the event. Spontaneous mutation, caused by an "error" in DNA replication, illustrates this cause for indeterminacy very well. The occurrence of a given mutation is in no way related to the evolutionary needs of the particular organism or of the population to which it belongs. The precise results of a given selection pressure are unpredictable because mutation, recombination, and developmental homeostasis are making indeterminate contributions to the response to this pressure. All the steps in the determination of the genetic contents of a zygote contain a large component of this type of randomness. What we have described for mutation is also true for crossing over, chromosomal segregation, gametic selection, mate selection, and early survival of the zygotes. Neither underlying molecular phenomena nor the mechanical motions responsible for this randomness are related to their biological effects.

 Uniqueness of all entities at the higher levels of biological integration.
 In the uniqueness of biological entities and phenomena lies one of the major

differences between biology and the physical sciences. Physicists and chemists often have genuine difficulty in understanding the biologist's stress of the unique, although such an understanding has been greatly facilitated by the developments in modern physics. If a physicist says "ice floats on water." his statement is true for any piece of ice and any body of water. The members of a class usually lack the individuality that is so characteristic of the organic world, where all individuals are unique; all stages in the life cycle are unique; all populations are unique; all species and higher categories are unique; all interindividual contacts are unique; all natural associations of species unique; and all evolutionary events are unique. Where these statements are applicable to man, their validity is selfevident. However, they are equally valid for all sexually reproducing animals and plants. Uniqueness, of course, does not entirely preclude prediction. We can make many valid statements about the attributes and behavior of man, and the same is true for other organisms. But most of these statements (except for those pertaining to taxonomy) have purely statistical validity. Uniqueness is particularly characteristic for evolutionary biology. It is quite impossible to have for unique phenomena general laws like those that exist in classical mechanics.

3) Extreme complexity. The physicist Elsässer stated in a recent symposium: "[an] outstanding feature of all organisms is their well-nigh unlimited structural and dynamical complexity." This is true. Every organic system is so rich in feedbacks, homeostatic devices, and potential multiple pathways that a complete description is quite impossible. Furthermore, the analysis of such a system would require its destruction and would thus be futile.

4) Emergence of new qualities at higher levels of integration. It would lead too far to discuss in this context the thorny problem of "emergence." All I can do here is to state its principle dogmatically: "When two entities are combined at a higher level of integration, not all the properties of the new entity are necessarily a logical or predictable consequence of the properties of the components." This difficulty is by no means confined to biology, but it is certainly one of the major sources of indeterminacy in biology. Let us remember that indeterminacy does not mean lack of cause, but merely unpredictability.

10 NOVEMBER 1961

All four causes of indeterminacy, individually and combined, reduce the precision of prediction.

One may raise the question at this point whether predictability in classical mechanics and unpredictability in biology are due to a difference of degree or of kind. There is much to suggest that the difference is, in considerable part, merely a matter of degree. Classical mechanics is, so to speak, at one end of a continuous spectrum, and biology is at the other. Let us take the classical example of the gas laws. Essentially they are only statistically true, but the population of molecules in a gas obeying the gas laws is so enormous that the actions of individual molecules become integrated into a predictable-one might say "absolute"-result. Samples of five or 20 molecules would show definite individuality. The difference in the size of the studied "populations" certainly contributes to the difference between the physical sciences and biology.

#### Conclusions

Let us now return to our initial question and try to summarize some of our conclusions on the nature of the causeand-effect relations in biology.

1) Causality in biology is a far cry from causality in classical mechanics.

2) Explanations of all but the simplest biological phenomena usually consist of sets of causes. This is particularly true for those biological phenomena that can be understood only if their evolutionary history is also considered. Each set is like a pair of brackets which contains much that is unanalyzed and much that can presumably never be analyzed completely.

3) In view of the high number of multiple pathways possible for most biological processes (except for the purely physicochemical ones) and in view of the randomness of many of the biological processes, particularly on the molecular level (as well as for other reasons), causality in biological systems is not predictive, or at best is only statistically predictive.

4) The existence of complex codes of information in the DNA of the germ plasm permits teleonomic purposiveness. On the other hand, evolutionary research has found no evidence whatsoever for a "goal-seeking" of evolutionary lines, as postulated in that kind of teleology which sees "plan and design" in nature. The harmony of the living universe, so far as it exists, is an a posteriori product of natural selection.

Finally, causality in biology is not in real conflict with the causality of classical mechanics. As modern physics has also demonstrated, the causality of classical mechanics is only a very simple, special case of causality. Predictability, for instance, is not a necessary component of causality. The complexities of biological causality do not justify embracing nonscientific ideologies, such as vitalism or finalism, but should encourage all those who have been trying to give a broader basis to the concept of causality.

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## Physiological Implications of Laser Beams

The very high radiation flux densities of optical masers point to important biomedical applications.

Leonard R. Solon, Raphael Aronson, Gordon Gould

Development of molecular amplifiers in the visible and near-visible region (1) of the electromagnetic spectrum has been in progress at several laboratories. Such amplifiers go under the designation of "laser" or optical maser, the former term being an acronym for

light amplification by stimulated emission of radiation. Such devices have been successfully demonstrated at several places (2), and several industrial organizations have made them available commercially. It is almost certain that lasers will be incorporated into communications and other technologies at a rapid rate. This article presents some preliminary calculations which are of physiological interest in terms of the hazard associated with laser beams and their potential employment as biological and clinical tools.

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#### **Properties**

From the point of view of physiological interest there are two important properties of laser beams, the extremely collimated character of the light and its high degree of monochromaticity. The collimation property implies the possibility of obtaining large energy densities in narrow beams. The optimum divergence angle of a laser beam,  $\phi_{\min}$ , is limited only by the wavelength of the light emitted and the diameter of the laser source in accord with the Fraunhofer diffraction relationship:

$$\phi_{\min} = 2.44 \, \lambda/D_L \tag{1}$$

Here  $\lambda$  is the wavelength of the emitted laser light and  $D_L$  is the diameter of the beam emerging from the laser source or from a subsequent lens system, if one is used.

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The spectral line of laser light is potentially much narrower than the spectral lines achievable by ordinary excitation processes in gas discharge tubes or arcs, which are limited by the Doppler widths of spontaneous radiative transitions of individual atoms. Laser light, comprised as it is of coherent superposed wave trains emitted during induced transitions, is not so limited. Spectral lines narrow as the power of the laser source increases; lines as narrow as  $10^{-6}$  of a Doppler width have been observed (3), as predicted by theory (1).

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In subsequent paragraphs we give approximate formulas for retinal spot size and light intensity under various conditions. Consider a laser source that gives an energy release of S joules per burst for a pulsed laser or of S watts for a continuously operated laser. The energy flux density or intensity is  $I = S/A_B$  where  $A_B$  is the cross-sectional area of the beam. At a distance r centimeters from the laser source (sufficiently great so that the laser can be regarded as a point source), I is also given by:

$$I = \frac{S}{A_n} \to \frac{S}{\Omega r^2} \tag{2}$$

where  $\Omega$  is the solid angle into which the laser light is delivered. For a small far-field angular beam width  $\phi$ ,

$$\Omega = \pi \phi^2 / 4 \tag{3}$$

The diameter of any beam of light may be decreased (increased), with corresponding angular magnification (minification), by an appropriate pair of lenses or mirrors (see Fig. 1). For such an afocal lens pair the relation  $D\phi = D'\phi'$  holds approximately, where D and D' are, respectively, diameters of the incident and exit beams and  $\phi$  and  $\phi'$  are angles between rays within the beams. That is, the angular distribution of light rays within the beam is magnified (minified) by such a lens pair.

When a beam is incident upon a pupillary area C (in square centimeters), an amount of light IC will actually enter the eye. Depending on the wavelength, more or less of this energy will be absorbed by the cornea, lens, aqueous, and vitreous structures before the light reaches the retina. According to Ludvigh and McCarthy (4), about 70 percent of the red light (7000 A) incident on the eye reaches the retina (Table 1).

Table 1. Light transmission through the human eye (4).

Color	Wavelength (A)	Transmission (%)
Red	7000	70
Orange	6000	61
Yellow	5800	59
Green	5000	49
Blue	4700	43
Violet	4100	10

When the fraction of incident light transmitted to the retina is designated by p, the intensity R at the retina is the total energy reaching the retinal divided by A, the area of the retinal image, or:

$$R = ICp/A \tag{4}$$

R is in joules per square-centimeter burst or in watts per square centimeter, depending upon whether the laser oscillator is pulsed or continuously radiating light. There are a number of special cases of interest which may be deduced from Eq. 4. Their discussion requires several parameters in addition to those previously defined.

The smallest angular displacement,  $\xi_{\min}$ , that can be resolved by the eye cannot be less than  $\xi_F$ , the angular resolution determined by the Fraunhofer diffraction pattern produced by the pupil, regarded as a circular aperture upon which plane wave radiation is incident. Using the Rayleigh criterion, one has

$$\xi_{\min} \ge \xi_{\rm F} = 2.44 \, \lambda/D_{\rm E} \tag{5}$$

where  $\lambda$  is the wavelength of the incident radiation and  $D_E$  is the aperture of the pupil. In a real eye, the retinal spot is larger than the Fraunhofer spot. It follows that, if f is the focal length of the eye, the minimum diameter  $h_{\min}$  of any retinal image spot is simply:

$$h_{\min} = f \xi_{\min} \tag{6}$$

In the subsequent discussion we also make use of the retinal spot angle  $\eta$ , which is the angular displacement sub-

tended by the retinal spot at the eye lens. By this definition, the diameter of the image on the retina h is given by:

$$h = f \tan \eta \simeq f \eta \tag{7}$$

Angle  $\eta$  may or may not be the same as the object angle subtended by the geometrical diameter of the laser source, depending upon considerations which will be made evident below. Specifying the object angle  $\theta$ , one finds from elementary optics that:

$$\tan \theta = D_{\rm L}/r$$

For small  $\theta$ ,

$$\theta \simeq D_{\rm L}/r$$
 (8)

Now for sufficiently small distances the eye may not be able to encompass the entire laser source because of the small angular divergence,  $\phi$ , of rays within the laser beam. Rays from the edge of the laser may not enter the eye. This would be true when

$$\theta = D_{\rm L}/r > \phi \tag{9}$$

However, the minimum effective image spot angle can never be less than  $\xi_{\min}$ .

If the object angle  $\theta$  is less than the laser beam angle  $\phi$  but greater than the minimum retinal spot angle  $\xi_{\min}$ , ( $\xi_{\min}$  <  $\theta$  <  $\phi$ ), then the image angle and object angle are equal:

$$\eta = \theta \text{ and } h = f\theta$$
 (10)

If the object angle is greater than the laser beam angle but the latter is greater than  $\xi_{\min}$ —that is,  $\xi_{\min} < \phi < \theta$ —the retinal spot angle is equal to the laser beam angle, or:

$$\eta = \phi \text{ and } h = f\phi$$
 (11)

If either  $\theta$  or  $\phi$  is smaller than  $\xi_{\min}$ , then  $h = f \xi_{\min}$ , as already mentioned.

In the ensuing paragraphs we shall consider the observer moving nearer to the laser source from a distant point under which the conditions of case A prevail.

Case A. This is the far-field case in

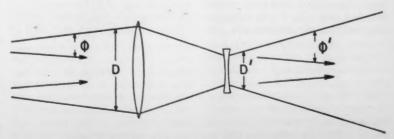


Fig. 1. Alteration of beam diameter by an afocal lens pair.

which the eye can see light from all parts of the laser but the retinal-image spot size is limited by the Fraunhofer diffraction pattern formed by the evethat is,  $\theta < \phi$ ,  $\theta < \xi_{min}$ . For the retinal energy density one has:

$$R = \frac{ICp}{A} = \frac{S}{\Omega r^2} \cdot \frac{4 Cp}{\pi h_{\min}^2}$$
$$= \frac{16SCp}{\pi^2 \phi^2 f^2 \xi_{\min}^2 r^2}$$
(12)

Making use of Eq. 5 and of C = $\pi D_{\rm E}^2/4$ , one has alternatively:

$$R = \frac{4SD_{\rm E}^4 p}{(2.44)^2 \pi \phi^2 f^2 \lambda^2 r^2}$$
 (12a)

Case B. This is the near-field case in which the laser beam can no longer be considered as coming from a point source. The retinal spot size will be larger than the minimum due to eye diffraction if both the object angle and the angle between rays in the beam are larger than the Fraunhofer angle of the pupil  $(\xi_{\min} < \theta, \phi)$ . Then the spot size is given by Eq. 10 or Eq. 11.

A more general formula for the retinal energy density or intensity, valid for case B as well as all other cases, is given by Eq. 13:

$$R = \frac{16SCp}{\pi^2 r^2 f^2 \phi^2 \theta^2 \xi^2_{\min}} \left[ \min(\phi, \theta, \xi_{\min}) \right]^2 \quad (13)$$

or

$$R = \frac{4S D_{\rm E}^2 p}{\pi r^2 f^2 \phi^2 \theta^2 \xi^2_{\rm min}} \left[ \min(\phi, \theta, \xi_{\rm min}) \right]^{\rm B} \quad (13a)$$

Here, min  $(\phi, \theta, \xi_{\min})$  is equal to the smallest of the three angles:  $\phi$ ,  $\theta$ , and  $\xi_{\min}$ . Note that R is inversely proportional to  $r^2$  in the far-field case, when  $\theta < \phi$ ,  $\xi_{\text{min}}$ , and is independent of r otherwise.

Case C. The beam may be smaller than the pupil as it enters the eye. This situation might obtain either because the laser diameter is smaller than the diameter of the pupil or because the beam diameter has been made smaller by a lens train (Fig. 1). In either case the spot size will be enlarged. The energy density or intensity in the spot focused on the retina will again be given by Eq. 13a if D<sub>B</sub> is taken to be the diameter of the beam passing through the pupil and r is the distance from the eye to the laser, or, if a lens system is employed, to the last lens.

The TRG Vireo I laser light, a pulsed ruby laser used in the animal experiments reported by Zaret et al. in this issue (5), has the following approximate values for the parameters previously discussed: S = 0.1 joule per burst;  $\phi = 0.005$  radian;  $\lambda = 7 \times 10^{-5}$  cm (6943 A);  $D_E = 1$  cm; and pulse duration = 0.5 msec. The range of DE in the normal eve depends principally upon accommodation to the level of illumination and varies from about 0.15 to 0.6 cm (6). From Eq. 5 we find, for a wavelength of about  $7 \times 10^{-6}$ cm, that  $0.00014 < \xi_F < 0.00057$  radian for 0.6 cm >  $D_{\rm E}$  > 0.15 cm;  $\xi_{\min}$  is somewhat larger than  $\xi_{F}$ , but in any case,  $\xi_{min} < \phi$  for the Vireo I. Taking  $D_E$  as 0.5 cm for purposes of calculation, one immediately infers that the critical distance re which separates the near-field case from the far-field case is given by

$$r_{\rm c} = \frac{D_{\rm L}}{\xi_{\rm min}} \tag{14}$$

The critical distance  $r_c$  is then somewhat less than

$$\frac{D_{\rm L}}{\xi_{\rm F}} = \frac{D_{\rm E}D_{\rm L}}{2.44\lambda} = 2.9 \times 10^{\rm s} \, {\rm cm}$$
 (15)

when  $D_E = 0.5$  cm is taken for purposes of calculation. Taking p = 0.7and f = 1.67 cm (7), one calculates for the near-field case  $(r < r_c)$  from Eq. 13 or 13a that R = 326 joules per square-centimeter per burst.

This is roughly the retinal energy density that would be delivered by direct viewing of the sun for about 1/2 minute (8) and about 6 times the energy density required to produce a retinal burn in the experiments of Eccles and Flynn (9). In these experiments the eyes of rabbits were exposed to telescopically concentrated sunlight. Different intensity rates were used for

various elapsed times. Eccles and Flynn made exposures at 6, 40, 50, and 70 calories per square centimeter per minute within the focused retinal spot. An exposure of 40 cal/cm2 min for 30 seconds appeared to be innocuous, while 50 cal/cm<sup>2</sup> min for the same period was likely to produce a retinal lesion. The latter exposure corresponds to an integrated intensity of about 100 joule/ cm2. On the other hand, the higher intensity for only 10 seconds, corresponding to an integrated intensity of 50 joule/cm² was sufficient to produce a lesion. At 6 cal/cm² min an exposure of 12 minutes was required to produce retinal damage-an integrated intensity of about 300 joule/cm2.

The existence of an intensity or energy density rate-dependence is clearly evident. It is probable that there is a short integration time within which damage is proportional to the integrated intensity, irrespective of the rate. If this time is very much shorter than 10 seconds, then the integrated intensity obtained with the 0.5-millisecond duration of the Vireo I laser pulse may be considerably more than 6 times that required to produce a retinal lesion.

We conclude that the laser, being an emitter of high-intensity light, is a new energy source to be explored with regard to its effects on ocular and other tissues with a view toward biomedical application. Furthermore, persons working with laser light sources should be alerted to the potential occupational hazard.

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### Science and the News

#### The Next Budget: The President Is Saying a Few Things He Cannot Really Believe

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The Administration has begun to pay a good deal of attention to domestic politics. For the next few weeks half the cabinet will be out of Washington traveling around the country to build up interest in the Administration's domestic programs. But if the Administration were really serious about some of the statements the President and his associates have been making about their fiscal policies, there would not be much of a domestic program in the next session of Congress, and not much point in sending the cabinet on the road to build up support for it. Welfare Secretary Ribicoff has been traveling all fall, devoting half his speeches to the need for more investment in education, but last week he cut \$20 million out of the money Congress had appropriated for the National Defense Education Act. This does not make sense in any obvious way, but the peculiar logic of politics makes some peculiar demands of the politician. There is a good deal of deliberate obfuscation going on, which reflects an inclination to blur the contrast between the Administration's view of fiscal responsibility and the public's view. The great majority of economists support the Administration's view, but the public, after all, has more votes. The result is that the Administration will talk about its devotion to balancing the budget until it becomes obvious the budget is not going to be balanced. This is pretty much the same reason that Rockefeller and Goldwater will insist that they are not candidates for the Republican nomination in 1964 until it becomes unavoidable to concede that they are: Why give your opponents a target to shoot at any sooner than necessary?

The budget situation at the moment is this: For fiscal 1961, ending next June, the government expects to take in \$82.1 billion and spend \$89 billion,

leaving a deficit of \$6.9 billion. It will probably turn out to be larger. For fiscal 1962, beginning next July, the Administration predicts an income of \$92 billion, and the President has announced his firm intention, "barring urgent and unforeseen defense needs," to submit a balanced budget to Congress, while his Secretary of the Treasury has been saving the time is not right for tax increases. The \$10 billion increase in receipts over fiscal '62 assumes no increase in tax rates, but a substantial increase in receipts as the economy recovers from the recession. This would allow the federal budget to rise \$3 billion in fiscal '63 and still be in balance without a tax rise. But Administration officials have been saying that the defense budget will be at least \$50 billion next year, which is \$3 billion more than last year. By ordinary logic this would mean that there could be absolutely nothing in the next budget for increased investment in education or science or anything else.

#### "Economy"

The Administration has been saying very little about what it will ask for in the next budget, but it will certainly ask for some things beyond the increase in defense spending. Under Eisenhower, who took a genuinely dim view of increases in federal spending, the budget, after a drop-off reflecting the end of the Korean War, rose by \$2 to \$3 billion a year, with most of the increases coming in domestic programs. Despite Eisenhower's current attacks on the "immorality" of budget deficits, his Administration produced deficits in five of its eight years. On this experience alone, there is no great expectation that the budget will be balanced next year without a tax increase. What suggests that there can be no expectation at all of a balanced budget next year is that it is most unlikely that the Administration would want a balanced budget even if it could be obtained.

The President's elaborately publicized

warning to his cabinet to keep down spending and Ribicoff's cuts in his own budget in response to the President's request may be good politics, but in the view of the majority of the country's economists, and of all the economists to whom the Administration looks for advice, it is bad economics. If put into effect, it would probably even be bad politics. The public apparently likes to hear its leaders talk of their devotion to a balanced budget, but there is very little indication that it cares much one way or the other what an Administration does about balancing the budget. Eisenhower's second term produced three unbalanced budgets. and one barely in balance, for a net addition to the federal debt of \$17 billion in 4 years. It does not seem to have hurt his popularity in any noticeable way or to have dimmed his reputation as a man devoted to fiscal integrity. What would hurt politically much more than an unbalanced budget would be another recession following on the heels of the one we are just coming out of, and another recession is what, if the Administration's economic views are correct, is likely to be the most obvious by-product of a balanced budget next year.

The view of the Administration, repeatedly stated, is that the main reason the 1960 recession followed so quickly on the heels of the 1958 recession was that the government had turned too rapidly from a large deficit in fiscal 1959 to a small surplus in fiscal 1960. The change from the stimulating effect of a deficit, pumping extra money into the economy, to a surplus, taking money out of the economy, came, in this view, before the economy had really recovered from the '58 recession. After that recession, the unemployment rate, a key figure in these calculations, never dropped below 5 percent. It had been 3 percent when Eisenhower took office, a reflection of the busy state of the economy under the stimulation of the deficits produced by the Korean War; after the 1954 recession, it never dropped below 4 percent; after the '58 recession it did not drop below 5 percent. The new Administration suspected that, without greater efforts to stimulate the economy than Eisenhower was willing to accept, this chronic and creeping unemployment would edge even higher. It regarded this trend as an intolerable one which would at worst develop into a real depression, and which at best would cause a great deal of hardship among the increasing force of jobless workers and at the same time rob the economy of the many billions of dollars in goods that it could be producing if the idle resources could be put to work. The situation was particularly disturbing to an Administration that believed there would have to be substantial increases in federal spending for defense, foreign aid, and education and science, and in fact for government generally, and which, therefore, was especially anxious to see the economy grow and provide an increasingly large tax base out of which to finance these projects.

In view of this, the Administration took office with the intention of not merely producing a deficit in the current fiscal year, which was widely regarded as inevitable no matter what Administration was in power, but of continuing with an expansionist fiscal policy, which means mainly running a deficit, beyond fiscal '62 and the expected upturn in the economy, in order to push the economy to a point reasonably near full employment. The Administration talked of a 4-percent unemployment rate as a target. As a longer range goal, it talked of a 3percent rate. In any case the test of whether the Kennedy Administration's economic policy was really to be substantially different from the Eisenhower Administration's was not whether it would incur a deficit in a year when it was almost unavoidable, but whether it would continue to push the economy higher after the popular view had come to be that the recession was over and the time had come for tightening up on government spending to avoid in-

For a few months after the new Administration took office, it looked as if it might conceivably be possible to avoid making this touchy policy decision, to which the Administration was intellectually committed, but which would be difficult to explain to the public. If the economy rose very quickly out of the recession, it might be in a sufficiently booming condition by the end of fiscal '62 to allow a balanced budget in fiscal '63, even under the Administration's economic views. Administration officials talked a great deal last spring about balancing the next budget.

Now, despite the elaborate publicity given to Kennedy's request to his cabinet members to hold down spending, and to Ribicoff's token cuts in the Health, Education, and Welfare budget,

the Administration is no longer talking of a balanced budget, but a budget that will be in balance on paper when submitted. There is a great difference. For fiscal '59, for example, Eisenhower's budget, when submitted to Congress, showed a \$500 million surplus which, by year's end, turned out to be a \$12.7 billion deficit.

Kennedy's talk of an intention, barring unforeseen defense increases, to submit a balanced budget must be interpreted in the same way as his talk immediately after taking office of not asking for any increases over Eisenhower's budget recommendation that would "of and by themselves" unbalance the budget. Probably no more this year than last do the President's remarks reflect anything more than a conventional response to the popular feeling that the President must always be in favor of balancing the budget, no matter how profoundly unwise he might believe it to be under the circumstances.

#### **Budget Talk**

The President's words must be interpreted very literally. Last year he meant just what he said about not unbalancing Eisenhower's budget, and not a bit more. The Wall Street Journal had called the final Eisenhower budget a "political joke on the incoming Administration," and it was easy enough for the new Administration to point out a number of peculiarities of the budget that suggested that the surplus Eisenhower had predicted was based on a combination of wishful thinking and rather carefree accounting. A minor example was that, although the President's message accompanying budget included a recommendation for building the Stanford linear accelerator, the money to begin work on the \$114 million project appeared nowhere in the budget itself. As a result the Administration could argue that Kennedy had lived up to his promise, since his recommendations for extra spending could not "of and by themselves" unbalance a budget that was really never in balance to begin with.

This year the President says that he intends to submit a balanced budget, but this is not to be interpreted to mean anything more than the minimum that it says; specifically, it does not mean that the President necessarily has any intention of having a balanced budget at the end of the year, only that he intends to submit a budget at the beginning of the year that, on paper at least, will be in balance.

The hard fact that lies in the way of a genuine effort to balance the budget is the familiar unemployment rate. In terms of output the economy is coming along nicely. Eisenhower's last budget predicted a gross national product for the current year of \$515 billion, a figure that was widely regarded at the time as overly optimistic. But the actual output for the year, it is now estimated, will be higher, about \$520 billion. So the Administration can claim that its fiscal policies have had a good effect on the economy, particularly since there has been very little inflation this year. Where the picture is not so rosy is on the unemployment side. In defending his stimulatory policies, Kennedy suggested last year that without extra federal spending to push up the economy, unemployment would "hover between 6 and 7 percent throughout the year." This would mean a million or two more unemployed workers above what there should be under reasonably full employment. What has happened, though, is that although the economy has been recovering well from the recession, the unemployment rate has shown no recovery at all. It has not hovered between 6 and 7 percent, but between 6.8 and 6.9 percent. We are producing more than ever before, but the unemployment rate is only now, 9 months after the upturn in the economy, beginning to show even modest signs of improving. There is a large body of workers whose jobs have been taken by machines, and the economy must grow faster if they are to be provided with jobs. In the face of this need for faster economic growth, there is no likelihood that the Administration would want to pass up the opportunity to stimulate growth by pumping more money into the economy through another deficit, particularly when it sees the extra spending as not only stimulating the economy, but as paying for programs that are thoroughly worthwhile in themselves. It will be interesting to see if the President does succeed in submitting a budget balanced on paper. If he does, it will surely be a nice display of ingenuity, but it is not to be taken very seriously. The real question, to which the Administration has as yet no answer, is not whether the Administration will now in the name of economy forget about the education programs it failed to get through Congress last year, but how, after last year's debacle, it expects to get the Congress to pass the programs this vear.-H. M.

## Soviet-American Exchanges: For Different Reasons, Both Sides Find Them Advantageous

Amidst the distrust and truculence that afflict East-West relations, the Soviet-American agreement on cultural, educational, scientific, and technical exchanges has fairly well achieved its modest goals. The current agreement, which runs for 2 years, expires 31 December, and negotiations for a new agreement are expected to start shortly in Washington; the indications are that for markedly different reasons each nation finds continuance of the program to be in its interest.

Although the implementation of the program stands out as one of the more hopeful achievements in efforts at Soviet-American cooperation, the program has been marked by frequent squabbles, charges of lack of good faith, and, in some areas, no activity whatsoever. Compared, for example, with the informal, heavy "exchange" traffic that flows naturally between this country and many noncommunist nations, the Soviet-American program is a carefully regulated trickle, constantly under the scrutiny of both governments. Compared with what existed before the agreement, the current traffic is a considerable achievement; prior to the agreement, exchanges were virtually nonexistent.

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The agreement that is now in effect has its roots in a limited exchange that developed in the balmy international atmosphere produced by the Geneva Conference in 1955. The reappearance of the East-West chill following the Hungarian revolt the next year blocked expansion of the program. In 1959. however, the two governments signed a 2-year agreement that, in the manner of two parties lacking faith in each other's intentions, detailed the exchanges, tit for tat. Under the agreement, the National Academy of Sciences was designated to work out scientific exchanges with the Academy of Sciences of the U.S.S.R. Semantically, this arrangement balanced nicely, but it was soon apparent that it matched a relatively small, nongovernmental body with what in effect is the holding company for much of the Soviet Union's gigantic scientific establishment. This disparity has led to considerable fric-

It is estimated that under the over-all agreement the exchanges between 1 January and 1 July 1961 involved about 3500 Americans going to the So-

viet Union and some 2700 Soviet citizens coming to this country. Included in the totals for these years are about 1000 American scientists and about 800 Soviet scientists. Relatively few of these scientific exchanges were carried out under the detailed inter-Academy agreement, which was not intended to be the only framework for exchange in this area. Accounting of the over-all totals is complicated by the budding East-West tourism which often involves individuals who combine business with personal travel. This category of exchanges is inevitably subject to various interpretations and has led to questions of good faith on both sides. American professionals traveling in the Soviet Union have not unnaturally on occasion sought to look up their Soviet counterparts. There is little doubt that this has almost invariably been a matter of individual enterprise. Soviet tourists here are very much under the scrutiny of their government, and when they turn out to be scientists seeking out their American counterparts, it is not unreasonable to assume they are following a design.

#### Soviet Aims

American officials associated with the program have noted that, not unexpectedly, the Soviets have employed the exchanges as a device for furthering their scientific, technical, and propaganda interests. A State Department review points out: "Most of the problems in exchanges with the Soviet Union flow from the nature of the Soviet system and the differing goals of the two countries. Apparently the Soviet government seeks, first, to gain scientific and technological information from this country, and second, to influence American public opinion more favorably toward the Soviet Union. Our long-term purpose is to reach as many of the Soviet peoples as we can with facts about this country and the truth about its policies and objectives. . . . Our short-term purpose is to find out as much about the Soviet Union and its society as we can, on the supposition that it is much safer to know well one's opponent and competitor. . . .

"The Soviet side pushes steadily for implementation of every possible exchange where it stands to gain information or increase its prestige; in the areas where it lacks interest—long-term or informational exchanges—it drags its feet and astutely places one impediment after another to implementation."

The principal American leverage for

assuring reciprocity is the visa authority, which assures complete control over the flow of Soviet visitors. Beyond this power, however, the U.S. has found that the limitation of information about Soviet society makes it difficult to pinpoint what we consider to be desirable exchanges. The reciprocity principle is applied relatively easily to exchanges of orchestras, athletic teams, and exhibits-though even in these areas the U.S. has had to raise the threat of restricting Soviet programs in response to attempts to limit American itineraries. In seeking to arrange equivalent scientific exchanges, however, the Academy here has found itself hampered by the secrecy that surrounds the Soviet scientific establishment. As one Academy official put it: "Soviet science is something of an iceberg. We are aware that there are vast areas, great scientific establishments, of which we know nothing. In some areas, we don't even know who their leading people are. On the other hand, except for those areas bound by military security, we are wide open, and anyone who is willing to make the effort can become well-informed about what is going on where in American science."

The desire to maintain this secrecy is believed to be responsible for Soviet recalcitrance in carrying out the inter-Academy agreement on exchanges at national scientific conferences. At such meetings, it is felt, personal contacts could develop that could lead to a better understanding of the Soviet scientific "iceberg." Since the agreement went into effect, however, the Soviets have shown little cooperation in exchanging lists of national conventions. Last year, the U.S. submitted a list of 23 meetings and waited 3 months before the Soviet list was forthcoming. The latter, it was found, contained only nine meetings, two of which had already taken place with Americans participating outside the inter-Academy agreement. Two others were executive meetings of international organizations, to which the U.S. had access through its membership. Another two were in the social sciences

An additional source of friction has been in the information exchange program. At the outset the program was hopefully looked upon by U.S. officials as a means for overcoming the traditional Soviet policy of preventing other nations from describing themselves to the Soviet people. One of the principal means for circulating information about this country was to be the

monthly magazine Amerika, a slick, picture publication, something in the format of Life, which was to be permitted a distribution of 50,000 in the Soviet Union in return for the same circulation here of a similar Soviet magazine, USSR. Both are sold through newsstands and subscriptions, and the observation of American officials has been that Amerika is immensely sought after by the Soviet people. In this country, however, slick magazine articles on the Soviet Union are not a novelty. USSR has encountered sales difficulties, and each month there has been a remainder of several thousand unsold copies. In retaliation for the return of the unsold copies, the Soviets have taken to sending back several thousand copies of Amerika as unsalable.

Advocates of a harsh line toward the Soviet Union have berated the exchange program as a form of espionage in which we knowingly permit the Soviets to tap our superior skills. They point to the fact that much of our traffic to the Soviet Union is pretty much on an unorganized basis and is largely determined by the professional interests and personal curiosities of the Americans who are involved; in contrast, there are indications that there is little hit or miss in Soviet interest in what is going on here. "Their efforts," an American official noted, "generally seem to be centrally directed to gaining specific information about fields in which we surpass them."

The counter argument is that the Soviets have learned virtually nothing about American science and technology that was not available to them from freely circulating publications. On the other hand, the exchanges, despite the impediments created by the Soviets, have for the first time given American specialists an opportunity to look at many previously hidden-away aspects of Soviet society. Moreover, it is naive to assume that the U.S. is bypassing opportunities to relate the fruits of the exchange program to the national security.—D.S.G.

#### Fish Flour: FDA Collects Comments on Protein Supplement

The fish flour controversy (Science, 29 Sept.) will soon arrive at the next stage on what promises to be a long and contentious route.

The 60-day period set by the Food

and Drug Administration for public comment on the high-protein food supplement expires Wednesday. FDA, which has informally indicated opposition to approving the product for sale in this country, will then study the comments before it issues an order in the case.

The product for which FDA approval is sought is made from whole fish, and is considered to be of great potential for ending protein deficiencies in many of the developing nations. Although the market in this country is regarded to be insignificant, the applicant, the VioBin Co., of Monticello, Ill., feels it would be at a psychological disadvantage in promoting the product abroad if it were not first certified for sale here. FDA approval, formally known as a "standard of identity," is not required for export. FDA has objected to whole fish flour on the ground that it contains parts of the fish not normally eaten in this country. The process reduces the fish to an odorless, tasteless powder, which blends easily with various foods.

The courses open to FDA are to approve VioBin's application as submitted, approve it with modifications, or reject it outright. In any case, parties that feel adversely affected by the decision have the right to a public hearing and eventually an appeal through the federal courts.

FDA reported last week that it had received more than 500 individual comments, including a considerable number from state public health authorities who share FDA's aversion to the product. Several fisheries organizations submitted letters of support.

Fish flour has received considerable attention in the Food for Peace agency, and its director, George McGovern, has expressed dismay at the FDA decision to subject the application to the long and uncertain review process.

There are indications, according to Food for Peace officials, that the agency will be placing emphasis on encouraging manufacture abroad, an awkward thing to do as long as another federal agency refuses to certify it as fit for human consumption at home.

The controversy has aroused the interest of several members of Congress, including Senators Douglas and Saltonstall. For the present they are content to let the FDA review run its course, but a number of members of the House have introduced a bill to exempt the product from FDA jurisdiction.

#### Birth Control: No Reaction to Revelation of NIH Role

Federal financing of research that bears directly on birth control was publicly disclosed last week for the first time. What was most remarkable, perhaps, was not the revelation, but the lack of any apparent adverse reaction to the disclosure of U.S. involvement in this politically sensitive area. The silence to date has encouraged advocates of population control in their view that a favorable climate of opinion is developing on the subject of the need for this country to seek solutions to the population problems of the developing nations.

The disclosure, contained in a brief article in *Newsweek*, outlined the conclusions of a confidential "Survey of Research on Birth and Population," which was produced by the National Institutes of Health. The survey found that NIH is currently spending the relatively modest sum of \$1.3 million on studies related to birth control. The expenditures of private organizations, foundations, and industry bring the annual total to an estimated \$5.7 million.

NIH, which has one of the most wide-open information policies of any government agency, has adamantly maintained in the past that none of its expenditures are for birth control activities. As recently as last July, the New York Times, on the basis of information from NIH, reported that NIH has "a budget this year of \$560,000,000 but not a cent is earmarked for what many consider one of the most serious public health problems in the world—the population crisis."

The NIH survey notes that "any basic research on the process of reproduction is at the same time research in birth control." Since 1955, it reports, the Human Embryology and Development Study Section has made 748 grants. Of the projects current last year, 146 "were found to be relevant, more or less closely, to birth and population control. Sixty-six of the 146 were rated as distinctly relevant." Their funding totaled \$976,386.

A statement accompanying the survey concludes that "The climate for research toward birth and population control appears to be undergoing definite change. Those who most keenly sense this change are hopeful that a research area that they feel has enormous public health importance will now receive its due attention."

#### Announcements

The 1961 Nobel prizes in science have been awarded to Georg von Békésy (medicine), Melvin Calvin (chemistry), and Robert Hofstadter and Rudolf Mössbauer (physics).

Békésy, 62, was cited principally for discoveries concerning the physical mechanisms of stimulation within the cochlea, the spiral canal of the inner ear. This work, performed in Hungary 30 years ago, demonstrated how the cochlea differentiates between various sounds. Hungarian born, Békésy was trained as a physicist at the University of Budapest, where he taught until the communists came to power in 1946. During this period (1923-1946), he also worked in the Hungarian Telephone Research Laboratory. He spent the following 3 years at the Caroline Institute in Stockholm. Since 1949 he has worked at Harvard as a senior research fellow in the psychoacoustic laboratory.

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Calvin, 50, was cited for his establishment of the sequence of chemical reactions involved when a plant assimilates carbon dioxide. This project, which he began about 15 years ago, utilizes radioactive carbon-14 to study the various chemical reactions that occur in plants during photosynthesis. Calvin received his doctorate in chemistry from the University of Minnesota in 1935. After 2 years of research at Manchester, England, on a fellowship grant, he joined the faculty of the University of California at Berkeley, where he is currently working.

Hofstadter, 46, was honored for his



Rudolf Mössbauer



Robert Hofstadter

studies of electron scattering in atomic nuclei and for discoveries concerning the structure of the nucleons. He received his master's and doctor's degrees in physics from Princeton and spent the early part of World War II at the National Bureau of Standards working on the proximity fuse. He became assistant professor of physics at Princeton in 1946 and, in 1950, joined the Stanford University faculty, where he is now head of the physics department. There he began the work with the university's linear accelerator that brought him the Nobel prize. During 1958-59 he spent a year on a Guggenheim fellowship as a guest professor at CERN, the European Organization for Nuclear Research, in Geneva.

Mössbauer, 32, who will share the physics prize with Hofstadter, was cited for his method of using radiating nuclei as accurate measures of time, making possible the first laboratory test of the theory of relativity. This effect, which now bears his name, is of fundamental importance in atomic research. Mössbauer was born in Munich. He worked for 2 years in an optical firm before entering Munich Technical Institute in 1949. There he received his master's degree in 1955 and his doctorate 3 years later. In 1960 he went to Pasadena as a guest on the staff of the California Institute of Technology, where he is currently employed.

#### Scientists in the News

Recent awards of the National Aeronautics and Space Administration:

Abe Silverstein, recently appointed director of the Lewis Research Center at Cleveland, Ohio, received the outstanding leadership award for formulating, effecting, and directing various elements of the agency's space program and for developing space flight centers.

William J. O'Sullivan, Jr., assistant to the chief of the applied materials and physics division of NASA's Langley (Virginia) Research Center, received the exceptional scientific achievement award for developing the Echo inflatable balloon satellite.

Theodore B. Davich, entomologist and a former director at the U.S. Department of Agriculture's entomology research division, College Station, Texas, has been appointed director of the USDA's newly organized Boll Weevil Research Laboratory in State College, Mississippi.



Georg von Békésy



Melvin Calvin

### **Book Reviews**

#### British Bridge

Science Survey. vols. 1 and 2. A. W. Haslett and John St. John, Eds. vol. 1, 1960, 360 pp., \$5.75; vol. 2, 1961, 372 pp., \$7.50. Macmillan, New York. Illus. + plates.

It has been said of Baron von Humboldt that he was the last man who encompassed, within his ken, all of science as it then existed. In the century since his death the frontiers of knowledge have expanded like the gas cloud of a supernova. Today even the well-educated layman no longer comprehends problems that, despite their complexity, affect his life deeply. This has led to the concept of "two cultures" set forth by C. P. Snow.

Among the more valiant attempts to bridge the gap was the publication, last year, of Isaac Asimov's Intelligent Man's Guide to Science [reviewed in Science 132. 1830 (1960)]. This two-volume work covered so broad an area that no one man could be fully informed of developments in all of the fields concerned. Hence there were some inaccuracies, but they detracted little from the total impact of that highly readable book.

Now we have another approach to the problem in the series of annuals, inaugurated last year, entitled Science Survey, prepared with the cooperation of the British Association for the Advancement of Science. In contrast to Asimov's work, each subject is dealt with by a specialist in the field. The two volumes that have appeared to date were edited by A. W. Haslett and John St. John.

A number of the chapters are based on papers or lectures presented to meetings of the British Association. In some cases they are reminiscent of the lead articles that appear in *Science* or in *Scientific American*. However the defi-

nition of "science" is extended to include such technological subjects as synthetic textile fibers and the degrees of annoyance caused in residential areas by jet planes taking off from New York International Airport. At the other extreme are chapters on relativity, stellar evolution, and the fundamental particles.

The subject matter, in some cases, has clearly not been chosen for its scientific importance, but rather for its appeal. In his foreward to the 1960 volume Sir George Thomson, then president of the British Association, notes that one of the association's paramount goals is "popularisation at all levels." Likewise, in the preface to the 1961 volume, Sir Wilfrid Le Gros Clark, who succeeded Sir George as president, cites the scientific education of young people as a special objective.

Because fallout and radiation dangers confront laymen with decisions that are particularly troublesome, three chapters of the first volume are devoted to this subject, calling to mind efforts by the American Association for the Advancement of Science to educate the public in this area.

Among the most interesting chapters are those on subjects that might be described as off-beat. These include one on animal courtships and another on the reasoning used to deduce the migration habits of eels and salmon. Progress in many fields is so rapid that some of the material already is dated. The second volume contains a postscript to the first, attempting to rectify this, but this can be done only to a limited degree. While contemporaneity is an asset, this series is chiefly valuable as an authoritative and at times highly entertaining exposition of the manner in which the scientific method is being applied to problems of our time.

WALTER SULLIVAN

New York Times

New Mathematical Library. vol. 1, Numbers: Rational and Irrational. Ivan Niven. viii + 136 pp. vol. 2, What Is Calculus About? W. W. Sawyer, viii + 118 pp. vol. 3, An Introduction to Inequalities. Edwin Beckenbach and Richard Bellman. x + 133 pp. vol. 4, Geometric Inequalities. Nicholas D. Kazarinoff. x + 132 pp. vol. 5, The Contest Problem Book. Charles T. Salkind. vi + 154 pp. vol. 6, The Lore of Large Numbers. Philip J. Davis. x + 165 pp. School Mathematics Study Group, New Haven, Conn.; Random House, New York, 1961. Paper, \$1.95. (Clothbound volumes available from Library Publishers, Chicago, III. \$2.95)

These are the first six titles of a new series, the New Mathematical Library, produced under the direction of the School Mathematics Study Group (SMSG). In the spring of 1958, after consulting with the presidents of the National Council of Teachers of Mathematics and the Mathematical Association of America, the president of the American Mathematical Society appointed a small committee of educators and university mathematicians to organize a study group whose objective would be to improve the teaching of mathematics in the schools. Edward G. Begle was appointed director of the group, which was called the School Mathematics Study Group, with headquarters at Yale University.

It is expected that eventually the New Mathematical Library will consist of more than 30 single-topic books that will be useful as supplementary reading material for high school students, teachers, and the interested lay public. These books are to be written by outstanding mathematicians. The SMSG Newsletter (No. 8, May 1961) states the three primary objectives of the monographs: (i) to disseminate good mathematics at the secondary school level which will supplement the usual high school curriculum, (ii) to awaken interest among gifted students, and (iii) to present mathematics as a satisfying, meaningful human activity. These first six books taken as a set certainly achieve these objectives for many students in grades 7 through 12. In general, the monographs are written so that the beginning sections can be understood by most stu-

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dents taking high school mathematics. The author of each book has indicated the background needed by the reader to be able to benefit from reading the book.

In general each volume starts in with elementary material that can be understood by many students in grades 7 through 12 and proceeds to develop the topic so that several sections at the end of each book require more mathematical maturity. These books are meant to be read with pencil in hand and time taken out to do some pencil work filling in steps left out in proofs and in solving many of the problems that are an integral part of the books. Teachers will find the volumes very valuable for supplementing their knowledge of the topics discussed.

In the "Note to the reader" at the beginning of each book the reader is told that he will need little technical knowledge to understand most of these books, but he will have to make an intellectual effort. I quote a section from a note to the reader that needs to be emphasized: "If the reader has so far encountered mathematics only in classroom work, he should keep in mind that a book on mathematics cannot be read quickly. Nor must he expect to understand all parts of the book on first reading. He should feel free to skip complicated parts and return to them later; often an argument will be clarified by a subsequent remark. On the other hand, sections containing thoroughly familiar material may be read very quickly. The best way to learn mathematics is to do mathematics, and each book includes problems, some of which may require considerable thought. The reader is urged to acquire the habit of reading with paper and pencil in hand; in this way mathematics will become increasingly meaningful to him.'

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Few of the topics discussed in these volumes are included in the so-called traditional courses in secondary mathematics. On the other hand, the newer mathematics programs used in many of the better schools contain at least the elementary aspects of the topics discussed.

Students who have studied the SMSG texts, the University of Illinois Committee on School Mathematics texts, materials developed at Ball State Teachers College, or comparable "modern" texts will find these books easier to understand than will most traditionally trained students.

Numbers: Rational and Irrational is a very well paced book, in that 7th graders can read and understand much of chapter 1 on natural numbers and integers and chapter 2 on rational numbers. Geometry and algebra are needed for chapters 3 and 4 on real and irrational numbers. Chapters 5, 6, and 7 require the background of a junior or senior. There is plenty here to challenge the gifted, and many sections of chapters 5, 6, and 7 are within the reach of average juniors and seniors.

What Is Calculus About? is sure to delight many students at the end of grade 9 and during the 10th grade. They should be able to do the first six chapters which end with simple maximum and minimum problems. Calculus is approached through the study of speed, velocity, and acceleration. Second-year algebra students have plenty of background for all of the material in this book.

An Introduction to Inequalities is a book that all seniors capable of college work should know quite a lot about. This is material not found in most "traditional" programs, but found in all of the newer mathematics programs.

Chapter 1, "Fundamentals," chapter 2, "Tools," and chapter 3, "Absolute value," which gives the axiomatic aspect of inequalities, should be read from grade 9 through 12. Chapter 4, "The classical inequalities," requires junior and senior sophistication in mathematics. Chapter 5, "Maximization and minimization problems," and chapter 6, "Properties of distance," are interesting and will require the algebraic facility of the better students. This book should challenge the student during all of his high school years.

Geometric Inequalities, a book that I recommend studying after or concurrently with An Introduction to Inequalities, is definitely for high school juniors and seniors and probably requires greater sophistication in mathematical knowledge and ability than any of the other five. This is a fascinating book, but not one that should be read in a hurry.

The Contest Problem Book contains the problems from the annual high school contests of the Mathematical Association of America as well as the keys and solutions to all problems. Problems for the last 10 years have been included, and a classified index helps to locate particular types of problems. Arithmetic as well as geometric and

algebraic problems are in the book, and some are within the scope of a 9th grader, while others will challenge the best senior. Math clubs may find that many of these problems will start very stimulating discussions in their meetings.

The Lore of Large Numbers is a book that will fascinate all from grade 7 through 12. Elementary algebra is needed very quickly, so only the gifted 7th grader will go very far, and he will skip much of the book. The first sentence at the top of page 29 is confusing because the word "between" is not defined. Sections 15 and 16, are a bit confusing; very careful reading and interpretation of the symbolism and the way it is used there is necessary.

These books should be available in all school libraries. Teachers should read and study them, and they should encourage their students to buy the ones they find most appealing, to work on them during the years of high school, and to see how nearly they can master the books by the end of their senior year.

Trade editions are being published for the regular book trade by Random House and are available at book stores and at many paperback outlets. SMSG is making the books available to secondary school students and teachers at a reduced price of 95¢ each by agreement with Random House.

Teachers may order these books from School Mathematics Study Group, Box 2029, Yale Station, New Haven, Conn. W. EUGENE FERGUSON

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#### Cosmochemistry

The Abundance of the Elements. Lawrence H. Aller. Interscience, New York, 1961. xi + 283 pp. Illus. \$10.

The theory and practice of deriving elemental abundances from terrestrial materials, meteorites, cosmic rays, interstellar material, normal stars, and nonnormal stars is outlined for each topic in separate chapters. The treatment of the first three topics is more or less descriptive. The treatment of the last three occupies half the book, is more analytical, and is useful to the active investigator in the fields of cosmology and geochemistry, who may be

unfamiliar with the basic principles of the relation between atomic emission and absorption spectra on the one hand and abundances, pressure, temperature, and excitation mechanisms on the other. In a following chapter, Aller gives several recent universal abundance compilations (which he has modified) and compares them with a universal compilation based primarily on stellar data. Discrepancies are discussed in terms of measurement difficulties and source material differences. In a final chapter the basic nucleogenic theories of B<sub>2</sub>FH and Cameron are outlined without the most recent bifurcations.

Because of rapid change, it is difficult to write a useful book in this field. Aller has used the opportunity offered by the room in a book to present the entire subject with superior organization and clarity. As a result, his work may outlast the rapid obsolescence of the abundance data which he presents and may be welcome and useful for several years (as it is now) as a supplementary text in the borderline subjects of cosmology and geochemistry.

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#### Scientific Go-between

The Human Use of the Earth. Philip Wagner. Free Press, Glencoe, Ill., 1960. ix + 270 pp. Illus. \$6.

Science may be a unitary effort of men to gain mastery over their world and themselves, but the various sciences are more often like camps fortified against each other and suspicious of communications across the no-man'sland that lies between them. We may therefore thank our common totemic ancestors for an intellectual broker like Philip Wagner who, as a human geographer, is committed to wandering between camps. Conceptual integration is not an easy task, and the resultant combinations sometimes exhibit signs of strain; but it is this effort at synthesis, above all, that makes this book in "both geographical and ecological" aspects, such attractive reading. To bring order out of chaos, the author has employed the scientifically economical (if hazardous) tool of typology, and the book may best be characterized as a

set of typologies, related so as to produce a cognitive map of adjacent scientific territories.

Man's symbiotic ties with other organisms (plants, animals, and other men) may be categorized as either obligate or facultative (chapter 1). These two categories are then combined with a typology of economies derived from Polanyi, to obtain a fivefold scheme of economies, seen as symbiotic types: (i) obligate subsistence with sporadic relations with outsiders; (ii) obligate subsistence with facultative arrangements for reciprocity; (iii) obligate subsistence with facultative redistribution; (iv) obligate subsistence with facultative market relations; (va) obligate redistribution with facultative marketing (the Soviet Union); and (vb) obligate marketing with facultative redistribution (the United States). Chapter 6 presents a taxonomy of artifical objects made by man, in which there is implicit a progression from simple elements to automatic devices and a concomitant increase in man's power over nature. This taxonomy is linked, via a chapter on factors in the spatial structuring of such man-made objects, to a typology of livelihood types and foodgetting forms (chapter 8). Wagner has, wisely perhaps, refrained from integrating this typology with his economic types, but the last two livelihood types (peasantry, commerce) appear to articulate with types iv to vb, above, and with the categories "consumers' economy" and "producers' economy" discussed in chapter 9. Chapters 3 and 4 are not essential to this chain of considerations, but they serve to acquaint the "earth-scientist" with the conceptual trappings of his hostile friends in the social science camp. From reading this book, I came away with the feeling that there is a science called human geography; this after some initial doubt.

Terminological quibbles should not be allowed to detract from the high quality of this work, but I arched my eyebrows at the use of "consumers' economy" and "producers' economy" and—especially—at the use of "capital" for all artificial things made by man. On the other hand, why does a geographer put the Totonac in Oaxaca and the Arapesh in southeastern New Guinea (page 44)? Relocation seems urgent.

ERIC R. WOLF

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#### Arbiter of Mankind's Goals

Toward a Science of Mankind. Laura Thompson. McGraw-Hill, New York, 1961. xxvii + 276 pp. \$4.95.

Any progress in applying what is known of man and his behavior to the solution of social tensions and conflicts deserves attention. During the past three decades a handful of anthropologists, most of them in England, Mexico. and the United States, have attempted to formulate practical programs for action in a variety of situations such as colonial administration, American Indian health, conservation of economic resources, and industrial personnel problems. In general, the proposals have met with skepticism from administrators, but a few successes have encouraged the "applied anthropologists" to continue their efforts.

Laura Thompson reviews the changes in anthropology's orientation that have permitted the inclusion of these aims, which represent a marked departure from former goals (and for many in the discipline, from their current goals). Instead of seeking further understanding of man and his behavior, Thompson argues that we know enough now to tackle the problems of "how to improve the welfare of whole communities and of . . . tribes, nations, and international groupings," and "the formulation of adequate norms or standards for the advancement of community welfare and for the development of community-oriented government administration." Her approach is eclectic, drawing on the insights and techniques of numerous disciplines, such as physiology, psychology, animal ecology, and conservation, as well as the social sciences. She is liberal with quotations and includes several case histories from her own previously published work; except for too frequent lapses into jargon, the book is stimulatingly written and will interest a broad spectrum of readers.

The major part of the book is devoted to proposing and explaining the "social-action research approach" that the author believes will permit anthropologists to direct human activities toward "scientifically based ideal goals." This is an extraordinarily optimistic attitude, proposing to solve all the basic problems of mankind. Optimism should not be discounted, and it is needed in any approach to the world's crises in human relationships. But there are risks

in placing pure research in a secondary position and in emphasizing applied research at its expense. Mere manipulative techniques can, with bureaucratic support, take on the guise of science. Many will doubt that the anthropologist-administrator should be made the final arbiter of mankind's goals. Thompson does not picture a Brave New World or a 1984, but the assumption that any group of scholars knows what is best for every community and nation presupposes an omniscience few will grant even a new, unified "science of mankind." Nevertheless. Thompson has done social science a real service in pointing out the promise of a broader approach, oriented toward today's pressing problems.

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#### Microclimatology

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Das Klima der bodennahen Luftschicht. Rudolf Geiger. Vieweg, Braunschweig, Germany, ed. 4, 1961. 646 pp. Illus.

Meteorologists and ecologists, agriculturists and foresters, conservationists and geographers, architects and planners should welcome this fourth edition of Geiger's textbook on microclimatology. Since its first appearance in 1927 this book has dominated the field. From a slender volume it has grown into an imposing tome. Its earlier editions, including the English translation of the second edition [reviewed in Science 126, 214 (1957)], have helped to stimulate work in microclimatology a great deal.

Even with a 30 percent expansion in this edition, including 1218 literature citations, the author still had to exercise considerable restraint in choosing his material. He has succeeded admirably. The appearance of Sir Graham Sutton's companion volume on micrometeorology made it possible to omit much of the basic theoretical material. But in the phenomenological realm the book is without equal.

The contents fall under a few primary headings: interaction of the surface with the adjacent air; heat balance in this surficial atmospheric layer; climatic interactions with fields and forests; special reaction of climate to orographic influences; and finally, relations of mi-

croclimate to humans and animals. G. Hofmann contributed a chapter on methodology of observations. This bare outline does not indicate the richness of the teaching material in this book. Some professor might even follow the whimsical suggestion to take students out in a glaze storm and, as a final examination, let them answer all the microclimatic puzzles nature might pose in these cases.

On the more serious side, I hope that Geiger's injunction is heeded; he urges man to change from the ignorant destruction of beneficial microclimates to the deliberate creation of favorable changes in housing and city planning, reforestation and water management, and farm production. Rational climatic modifications are certainly closer at hand near the ground than in the clouds.

Presumably because of language problems the rather extensive Russian literature in the field has not found a foothold in the book. Perhaps in this as in some other respects one might cast an eye into the future. There is little doubt that a few years hence a handbook on microclimate will be needed. It would be wonderful to contemplate that Geiger, the undisputed master in the field, might take the helm and assemble a team to tackle this job.

H. E. LANDSBERG

Office of Climatology, U.S. Weather Bureau

#### **New Books**

#### Biological and Medical Sciences

The Adrenal Cortex. G. K. McGowan and M. Sandler, Eds. Lippincott, Philadelphia, Pa., 1961. 238 pp. Illus. \$5. Proceedings of a symposium organized by the Association of Clinical Pathologists and held at the Royal Society of Medicine (London), 14-15 October 1960.

Advances in Blood Grouping. Alexander S. Wiener. Grune and Stratton, New York, 1961. 561 pp. Illus. \$11. Selected papers on immunohematology published by Wiener (mostly since 1954), arranged by topic, with some added comments.

Carter's Principles of Microbiology. Alice Lorraine Smith. Mosby, St. Louis, Mo., ed. 4, 1961. 603 pp. Illus. \$6.

Inhaled Particles and Vapours. C. N. Davies, Ed. Pergamon, New York, 1961. 506 pp. Illus. \$15. Proceedings of an international symposium organized by the British Occupational Hygiene Society, 1960.

International Review of Cytology. vol. 2. G. H. Bourne and J. F. Danielli, Eds. Academic Press, New York, 1961. 368 pp. Illus. \$11.

Medical and Biological Aspects of the Energies of Space. Paul A. Campbell, Ed. Columbia Univ. Press, New York, 1961. 500 pp. Illus. \$10.

A Mirror up to Medicine. A. C. Corcoran, Ed. Lippincott, Philadelphia, 1961. 521 pp. \$5.75. Selections from the writings of physicians and others, designed to portray medicine and the "medical mind" from every point of view: Hippocrates, The First Aphorism; MacMichaels, The Cane's Story of the Last Illness of Sir Isaac Newton; Sherrington, Man on His Nature.

Models and Analogues in Biology. Symposia of the Society for Experimental Biology, No. 14. Academic Press, New York, 1960. 262 pp. Illus. \$9.50.

Nerves, Brain, and Man. John Grayson, Taplinger, New York, 1960. 253 pp. Illus. + plate. \$5.

Nomina Anatomica. Revised by the International Anatomical Nomenclature Committee, appointed by the Fifth International Congress of Anatomists (Oxford, 1950), and approved by the Sixth and Seventh International Congress of Anatomists (Paris, 1955, and New York, 1960). Excerpta Medica Foundation, New York, ed. 2, 1961. 109 pp. \$3.75.

Pharmacognosy. Edward P. Claus. Lea and Febiger, Philadelphia, Pa., ed. 4, 1961. 565 pp. Illus. \$12.50.

The Physiological Regulation of Salivary Secretions in Man. Alexander C. Kerr. Pergamon, New York, 1961. 86 pp. Illus. \$6.50.

Poliomyelitis. Papers and discussions presented at the Fifth International Poliomyelitis Conference, Copenhagen, Denmark, 26–28 July 1960. Compiled and edited for the Congress. Lippincott, Philadelphia, 1961. 459 pp. Illus. \$7.50.

Proceedings of the Fourth National Cancer Conference. Sponsored by the American Cancer Society and the National Cancer Institute. Lippincott, Philadelphia, Pa., 1961. 788 pp. Illus. \$9. Held at the University of Minnesota 13–15 September 1960.

Progress in Surgery. vol. 1. M. Allgöwer, Ed. Karger, Basel, Switzerland, 1961. 271 pp. Illus. \$15.

Protein Structure. Harold A. Scheraga. Academic Press, New York, 1961. 319 pp. Illus. \$8.

The School of Pharmacy of the University of North Carolina. A history. Alice Noble. Univ. of North Carolina Press, Chapel Hill, 1961. 247 pp. Illus. \$5.

Symposium on Water and Electrolyte Metabolism. C. P. Stewart and Th. Strengers, Eds. Elsevier, New York, 1961 (order from Van Nostrand, Princeton N.J.). 205 pp. Illus. Symposium organized by the Netherland Society of Clinical Chemistry and the Netherlands Society for General Pathology; held in 1960.

Transactions of the Society of Rheology. E. H. Lee, Ed. Interscience, New York, 1961. 382 pp. Illus. \$10.50.

Treatise on Invertebrate Paleontology. Pt. Q, Arthropoda 3. Crustacea, Ostracoda. Raymond C. Hall, Ed. Geological Soc. of America, New York; Univ. of Kansas Press, Lawrence, 1961. 465 pp. Illus. \$11.50.

## Reports

#### **Cerebral Dysfunction and Intellectual** Impairment in Old Age

Abstract. There is a marked decline in some intellectual abilities in old age. It is frequently hypothesized that impaired cerebral physiology accounts for some of this deficit. In old age the critical flicker frequency, a measure sensitive to cerebral dysfunction, is correlated with aging intellectual abilities. This is interpreted as evidence supporting the above hypothesis.

The average performance of the elderly on tests of certain intellectual abilities is markedly inferior to the average performance of the young. Old people usually experience particular difficulty with tests involving the acquisition of new knowledge and the utilization of new work methods (1). It is commonly alleged that alterations in cerebral physiology are one of the causes of this inferior performance. Although this is a plausible hypothesis, it is a difficult one to test, because detailed post-mortem examination of the brains of "normal" elderly people is a timeconsuming process beset with sampling and technical problems. However, an alternative approach would be to utilize in vivo procedures which are sensitive to subtle alterations in cerebral physiology. One such measure is the critical flicker frequency for intermittent light.

An extensive literature demonstrates that flicker-fusion frequency is lowered in many cases of dysfunction of the central nervous system. It is also well established that flicker-fusion frequency declines with age, the rate of decline resembling that of some intellectual abilities (2). The lower frequency in old age cannot be explained by changes in the optical system of the eye, but appears to be due in substantial part to changes in the neuroretina, optic tract, and geniculocalcarine system (3). This suggests a relationship between critical flicker frequency and declining intellectual ability. Elderly individuals with a comparatively high critical flicker frequency should have less impairment of the central nervous system and therefore less intellectual deficit than those of the same age with low flicker-fusion frequency. But a number of studies have failed to demonstrate a relationship between the critical flicker frequency and intellectual ability in healthy young adults whose intelligence ranges from dull normal to very superior (4). Therefore, if such a relationship exists in old age, the interpretation of its meaning is not so ambiguous as might first appear; it would be presumptive evidence for the role of cerebral dysfunction in the impairment of intellectual ability in old age.

While studying the effect of age on flicker-fusion frequency in a group of 40 men (65 to 95 years), Colgan (5) correlated the frequency with scores from the Wechsler-Bellevue intelligence test. When the influence of age differences within the sample was removed by the partial correlation technique, the r between critical flicker frequency and Wechsler-Bellevue was 0.36 (p < .05). We sought to substantiate Colgan's finding, employing 50 elderly women in a more restricted age range (74 to 80), carefully eliminating those with ophthalmological and other diseases known to affect flicker-fusion, and using only psychological tests with a marked age decline. In this study (3) scores from the Digit Symbol subtest of the Wechsler Adult Intelligence (WAIS), the Primary Mental Abilities (PMA) Reasoning Test, the Raven

Progressive Matrices, and the Wisconsin Card Sorting Test (WCST) correlated significantly with the critical flicker frequency, while the Porteus Maze did not.

The present report concerns the attempt to confirm our findings in a comparable group of male subjects, to provide an over-all evaluation of the combined data from the two studies, and to consider the implication of the results for the view that cerebral dysfunction accounts for some of the intellectual deficit of old age.

Detailed descriptions of the female subjects, the instrument used for measuring the critical flicker frequency, and the testing procedures have been presented elsewhere (3, 6). The male sample consisted of 36 men (68 to 80 vears old) drawn either from the same residential homes as the women or from three day-centers for the aged in New York City. Because of irregularity in attendance at the day centers, the number of men who completed the various tests ranges from 16 to 32. The greater difficulty in obtaining male subjects is typical in gerontological studies. However, it was considered inadvisable to lower the rigid selection criteria, especially those excluding individuals with eve diseases known to affect flickerfusion. Thus, more than 40 men were eliminated because ophthalmological examination revealed such pathology as cataracts, glaucoma, vitreous opacities, and macula degeneration (7).

Pearson product-moment correlation coefficients were computed between critical flicker frequency and scores from the five tests of intellectual abilities. Table 1 lists the correlations obtained in the male, female, and com-

Table 1. Pearson product-moment correlation coefficients between critical flicker frequency and five tests of intellectual abilities. of significance are one-tailed. Italics indicate partial correlation coefficients, removing the influence of age differences where both the test and critical flicker frequency were correlated with age in the sample.)

Test	Female	Male	Com- bined
Digit Symbol	0.36*	0.30†	0.33*
Porteus Maze	.17	.22	.201
PMA Reasoning (untimed)	.29†	.06	.231
PMA Reasoning (timed)	.27†	.51†	.32*
Raven Progressive Matrices	.32†	05	.07
WCST, categories completed	.22	.39†	.29
WCST, perseverative errors	54*	40t	46

<sup>\*</sup> n < .01. †p < .05.

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Instructions for preparing Reports. Begin the report with an abstract of from 45 to 55 words. The abstract should not repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper.

Type manuscripts double-spaced and submit

rype manuscripts double-spaced and submit one ribbon copy and one carbon copy. Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references

and notes.

Limit illustrative material to one 2-column figure (that is, a figure whose width equals two col-umns of text) or to one 2-column table or to two

dams of tear) of to the executating the consist of two figures or two tables or one of each.

For further details see "Suggestions to contributors" [Science 125, 16 (1957)].

Table 2. Intercorrelations and centroid factor loadings.

	Test	1	2	3	4	5	6	7	1	II	$h^2$
1)	Critical flicker										
	frequency		.37	.23	.23	.12	49	12	.47	38	.36
2)	Digit Symbol			.43	.65	.55	53	27	.78	.08	.61
3)	Porteus Maze				.44	.48	45	20	.61	.07	.38
4)	PMA Reasoning										
	(untimed)					.67	40	18	.73	.39	.69
5)	Raven Progressive										
	Matrices						38	32	.72	.39	.67
6)	WCST, perseverative										
-	errors							.34	71	.35	.62
7)	Age								40	.16	.19

bined samples. The results with the male sample generally confirm those of the earlier study, the most striking exception being the failure of the Raven Progressive Matrices to correlate with flicker-fusion frequency. When the data from the two studies are pooled to provide a larger sample, all the tests except the Progressive Matrices correlate significantly with critical flicker frequency. A centroid factor analysis of the correlations from the combined sample is presented in Table 2. The analysis yielded only one significant factor, a general intellectual one in which both critical flicker frequency and age have significant loadings.

In the combined sample the perseveration score on the Wisconsin Card Sorting Test correlated the highest with critical flicker frequency. This test measures rigidity in concept formation, and it is tempting to draw similarities between conceptual perseveration and the neurophysiological perseveration reflected in flicker-fusion. However, the failure of the factor analysis to uncover a perseverative factor somewhat inhibits such speculation.

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More than 20 percent of the variance in conceptual perseveration can be accounted for by flicker-fusion, presumably because both functions are sensitive to alterations in cerebral physiology. This relationship in the elderly might be explained by the comparative absence in some, and presence in others, of varying degrees of subclinical cerebral dysfunction. The relationship was probably attenuated by the exclusion of subjects with ophthalmological and neurological diseases and those in poor health. It is likely that these latter groups contained a disproportionate number of individuals with both low critical flicker frequency and severe intellectual impairment.

The results of the present study indicate the desirability of including measures of the flicker-fusion in longitudinal studies of aging. Repeated measurements throughout the life span of an individual would elucidate with less ambiguity the precise relationship between an individual's decline in intellectual ability and his decline in critical flicker frequency-and (presumably) in neural functioning.

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- George McDonald performed the ophthalmological examinations. We are indebted to the officials of the following institutions in New Ornicals of the following institutions in New York City for providing the subjects for this experiment: the Mary Manning Walsh, Joseph-ine Baird, and St. Patrick's homes, and the homes of the Little Sisters of the Poor in Manhattan, the Bronx, and Brooklyn; and also the Hodson, Sirovich, and Forest Community Day Centers. This research was supported by grant No. M-1283 from the National Institute of Mental Health, U.S. Public Health Service.

29 May 1961

#### **Humming: A Vocal Standard** with a Diurnal Variation

Abstract. The process of humming can be used as a basal vocal measurement which can be repeatedly obtained with an accuracy comparable to that of other physiological variables. Studies have shown a diurnal fluctuation of the hum frequency. Data were collected by employing automatic telephone-answering equipment.

Various studies have been made in an attempt to find correlations between vocal response and physiological change. A review of these studies suggests that one possible obstacle in this field has been the difficulty in establishing a standard vocal response which can be repeated with some consistency.

In order to achieve a vocal base line. it is important to reduce the number of variables associated with the functioning of the vocal mechanism. For example, during phonation the vocal cavities are altered by the relative positions of the tongue, mouth, and lips and also, to some extent, by the facial expression. In the study reported here, vocal samples were recorded in the laboratory and over the telephone to test the hypothesis that the process of humming can be used as a vocal standard. Subjects were asked to hum-while seated in a relaxed position with the mouth and lips closed-one continuous note for up to 10 seconds. The response was recorded on a continuous loop of tape. This procedure insured that the positions of the oral and nasal cavities at the time the vocal samples were taken were relatively constant.

The fundamental frequency was measured in the following way. The hum sample was played back on the tape recorder. The output of the recorder was displayed on the vertical axis of a cathode ray oscilloscope, while the output of the audio oscillator was fed to the horizontal axis, the two curves forming a Lissajous figure. Because vocal samples fluctuate, in some cases by a few cycles per second, about a mean frequency, the average hum frequency was determined when the oscillator was adjusted so that the twisting Lissajous figure turned approximately one way for half the duration of the cycle and in the reverse direction for the remainder of the cycle. To determine the relative intensity for each recorded sample, the average signal level was read from the standard VU meter.

Statistical analysis of the results (from 33 subjects) showed that when samples of the fundamental hum frequency were taken over periods up to 179 days, the coefficient of variation of the hum frequency ranged from 3 to 18 percent. Intensity readings for the same group over the same period gave coefficient-of-variation values of 32 to 300 percent. Table 1 shows the means and the standard errors for coefficients of variation of these results as compared with the calculated coefficients of variation of biochemical determinations; the data indicate that a basal vocal hum frequency can be repeatedly established with accuracy comparable to that obtainable for biochemical determinations.

The coefficient of variation for hum

Table 1. Means and standard errors for coefficients of variation of oral temperature, hum frequency, hum intensity, and the sodium and potassium concentrations in urine, sweat, and saliva

Item	Coefficient of variation (%)
Urine (Na)*	9 ± 3
Urine (K)*	$11 \pm 3$
Sweat (Na)*	$33 \pm 7$
Sweat (K)*	$20 \pm 5$
Saliva (Na)*	$22 \pm 2$
Saliva (K)*	$8 \pm 1$
Oral temperature†	$0.6 \pm 1$
Hum frequency‡	8 ± 1
Hum intensity‡	$101 \pm 27$

†As evaluated from readings or oral temperature studies (see 5). ‡As calculated from readings from 33 female subjects taken over periods up to 179 days.

intensity (101 ± 27 percent) is much higher than that for frequency (8 ± 1 percent), and this suggests that the relatively large fluctuations of intensity tend to mask subtle changes brought about by physiological mechanisms.

In a study to explore the diurnal fluctuation of the hum frequency, 18 female subjects telephoned the laboratory at three specified times during the day-(i) in the early morning, immediately after awakening (6:30 to 7:45 A.M.); (ii) at 12 noon, before lunch; and (iii) at the end of the day, before retiring for the night. The telephone calls were answered automatically and recorded on a Western Electric telephone-answering set, type I-BA, which made the following prerecorded announcement: "Please be seated; when you hear the beep tone at the end of this announcement please say your telephone number, the time, then hold the telephone close to your mouth, keep your lips pressed together in a comfortable way, and hum one note continuously for about 5 seconds. Thank you."

An analysis of variance of the data obtained for these 18 subjects showed that a definite diurnal fluctuation of the hum frequency occurred (P < .001). Subsequent tests revealed that the hum frequency was significantly higher at noon (241  $\pm$  11 cy/sec) than it was in the early morning (208 ± 7 cy/sec; P < .001). Moreover, the noon reading was significantly higher in frequency than the night reading (212  $\pm$  8 cv/sec: P < .001). No significant difference was found between the night reading and the early morning reading (.70 > P)> .60). This finding is undoubtedly influenced by restricting the various vocal parameters so that the acoustical signal is modulated solely by physiological change.

The diurnal fluctuation of the hum frequency suggests that this variable is associated with the sleep-wake cycle, as are many other physiological funtions. This can be deduced from studies by Carhart (2) who concluded that the increased breath pressure and increased tension on the vocal cords produce a rise in laryngeal frequency. Mitchinson's x-ray studies (3), showed that in humming the vocal folds become elongated with an increase in vocal pitch, while Sonninen (4) showed that a lengthening of the external larvngeal muscles and the cricothyroid muscle occurs when there is a rise in the pitch of the singing voice.

From the studies of Mitchinson and Sonninen and from those reported here it can be assumed that during the day there is a rise in breath pressure, with a consequent rise in tension of the vocal cords. There is also a lengthening of the laryngeal muscles and the cricothyroid muscle, all this resulting in a rise in the hum frequency (7).

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9 June 1961

#### Localized Cooling in the Brain

Abstract. A slender refrigeration probe for the production of reversible discrete lesions within the central nervous system of man and experimental animals is described. Cooling, in the region of the third nerve nucleus in cats, produced pupillary dilatation which was quickly reversed when the temperature around the third nerve nucleus returned to normal.

Localized cooling of structures deep within the brain is a relatively easy, inexpensive, and effective method of producing reversible brain lesions. The widespread use of stereotactic surgical techniques for the treatment of Parkinson's disease in man has made it im-

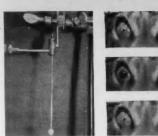


Fig. 1. (Left) Refrigeration probe with ice sphere around its tip. (Right) Pupillary size of the cat's eyes before (top), during (middle), and after (bottom) cooling produced by the refrigeration probe, 4 mm from the third nerve nucleus.

perative to find a safe, effective method of producing reversible brain lesions to guide the surgeon in placing his permanent therapeutic lesions in the thalamus and basal ganglia. A refrigeration probe seems to be one answer to this problem. Furthermore, this probe could give animal neurophysiologists a dramatic new tool for the investigation of the central nervous system. This is particularly true if it could provide the experimenter with one probing electrode that could record information, stimulate the brain, and make both reversible and permanent lesions. It was with both clinical and experimental objectives in mind that we designed a long, slender refrigeration probe.

The probe (Fig. 1, left) made for us by John Chato of Massachusetts Institute of Technology (1) consists of two stainless-steel needles. The outer needle is 125 mm long with an outside diameter of 1.6 mm. Its distal tip, containing 5-mm-long cooling chamber, is rounded for insertion into the brain. Its proximal end is attached to a small chamber which serves as an inlet for the liquid refrigerant (Freon 12). A smaller needle of 1 mm outside diameter lies within the larger needle; its distal tip has a beveled shoulder, which is elevated and lowered against the inlet to the cooling chamber by a knurled thumb screw at its proximal end. This device controls the inflow of refrigerant from the outer needle into the cooling chamber. The inner needle also serves as an exit for the expanded gas from the cooling chamber; it carries this cold gas up to the center of the probe and thus prevents cooling of the outer walls of the probe which carry down the uncooled refrigerant.

Our next problem was to see whether this probe would produce reversible lesions under experimental conditions. For this purpose, we did a series of ex0

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periments with cats, stereotactically placing the probe within 3 or 4 mm of the third nerve nucleus on the right side. Thermocouples were attached to the refrigeration probe at 1 and 3 mm away from the tip. We then photographed the cat's eyes before, during, and after the temperature of the probe was lowered to about 5°C (Fig. 1, right). We did not reduce the temperature of the probe to 0°C for fear of producing irreversible lesions about the tip of the probe. (2). Bright illumination of both pupils was constantly maintained throughout the experiments. Within 20 seconds, the ipsilateral pupil fully dilated and the contralateral pupil partially dilated. Within 45 seconds after the probe was turned off, the pupils returned to normal size. This process of cooling and warming was repeated in each cat at least three times (with cooling periods of up to 10 min) without altering the physiological results or time course of the localized brain cooling. In three cats with similar electrode placements near the third nerve nucleus, the results obtained were exactly the same.

For clinical use, Cooper and his associates (3) have introduced a small balloon into the tip of their brain probe. They feel that they can make temporary brain lesions by expanding the balloon and mechanically compressing brain tissue within the thalamus and basal ganglia. They have used this successfully in many hundreds of cases. The expanded balloon, however, has caused hemorrhage in some clinical cases, and thus, whether it can produce temporary lesions within the brain safely is in some doubt. Procaine injections have also been used to produce temporary interruptions of brain function in man. The injection of procaine into the thalamus or basal ganglia has two disadvantages. First the diffusion of a liquid in the center of the brain mass is somewhat unpredictable, and the physiological results of such interruptions are difficult to interpret. Secondly, the seepage of procaine or other local anesthetic agents into the brain ventricles may produce a clinical catastrophe. The use of a single beam of ultrasound for the production of reversible brain lesions has been described (4). This is an expensive and complicated tool for routine clinical use, and in experimental work it precludes the use of electrical recording devices at the site of the intended lesion. It is, however, another promising method of producing reversible brain

Although the brain tolerates heat very poorly (irreversible lesions can be made in the brain substance by heating it to 55° or 60°C), cold is tolerated more readily. The entire body temperature during surgery has been reduced to as low as 10° or 15°C for more than 44 minutes without discernible impairment in brain function (5). A localized decrease in brain temperature and its effect on conduction times and somatic and synaptic potentials will be a subject of continuing investigation in this clinic. We are also attempting to build a more slender semiconductor probe for brain cooling (6).

Note added in proof: It has come to our attention that a cooling probe was used to make lesions in the cerebral cortex of cats by Balthasar in 1957 [E. Balthasar, Deut. Z. Nervenheilk. 176, 173 (1957)1.

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Reduction of probe tip temperature to 0°C or below would permit rapid freezing of small amounts of subcortical brain tissue for biochemical analysis.

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6. This research was supported by the United Cerebral Palsy Foundation and by a grant from the National Institute of Neurological Diseases and Blindness. This paper was presented by one of us (V.H.M.) at the meeting of the New England Neurosurgical Society, Dedham, Mass., 9 June 1961.

19 June 1961

#### **Functional Effects of Focused Ultrasound on Mammalian Nerves**

Abstract. Differential blocking of conduction in mammalian nerve fibers has been produced by irradiation of the whole nerve with focused ultrasound. The smallest (C) fibers are the most sensitive; the largest (A-alpha) fibers are the least vulnerable. Fully reversible blocking can obtained with carefully graded doses of ultrasound.

Studies of frog sciatic nerve have revealed that the alpha, beta, and gamma fibers in the nerve are differentially sensitive to focused ultrasound (1). The effects of ultrasound upon fibers in

a wider size range have now been investigated (2), in studies of saphenous nerve of the cat. This is a skin nerve containing the alpha and delta subgroups of the A fibers (with diameters of 6 to 14 and 1 to 5 u, respectively) and a good representation of C fibers (of  $1 \mu$  or less).

In cats anesthetized with pentobarbital sodium, the saphenous nerve was exposed for 8 to 10 cm. Near its origin in the upper thigh and in the middle of the leg it was severed and freed from surrounding connective tissue, so that it could be lifted on stimulating and recording electrodes. Ultrasound (3) was directed at the midportion of the nerve. The ultrasound was administered in pulses of 0.4- to 0.9-second duration with a 2- to 3second interval between pulses.

Action potentials were recorded monophasically and after amplification were displayed on an oscilloscope. In each experiment the intensity (plate voltage of the ultrasonic generator) and duration of irradiation were increased gradually until alterations in the action potentials were noted. Before each irradiation several compound action potentials, with alpha, delta, and C fiber deflections, were photographed as controls. Records were also taken during the period of irradiation and afterwards during recovery from it.

As in the experiments on frog nerve fibers (1), it was found that focused ultrasound would abolish conduction of impulses completely and irreversibly if irradiation was sufficiently intense or prolonged. Fully reversible effects could be obtained with graded doses of lower intensity. Experiments were devoted chiefly to producing differential blocking of fibers of different sizes. To this end the administration of ultrasound was deliberately varied in order to explore the effects of different combinations of intensity, duration, pulse interval, and train length.

Figure 1 illustrates the results obtained in one of the most successful attempts to block differentially. Four columns of records are shown (Fig. 1, A to D). The upper and lower pairs of tracings in each were obtained before and after irradiation, respectively. The upper channel in each pair was recorded at high amplification.

Figure 1, column A, shows the effect of a train of 20, 0.5-second pulses of ultrasound at a plate voltage of 700. The C fiber deflection (4), indicated by the arrow, in the upper tracing was abolished during the course of this ir-

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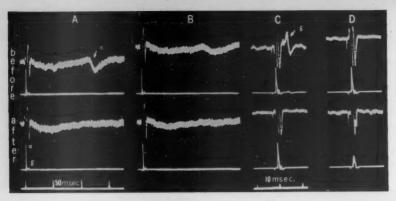


Fig. 1. Oscillographic records of compound action potentials in the saphenous nerve of the cat, showing the effects of irradiation of the nerve with focused ultrasound. The tracings in columns A to D were photographed at four different times in the course of a series of irradiations. The upper pair of tracings in each column were obtained before, the lower pair after, particular irradiations which blocked conduction differentially. In each pair the upper record is at higher gain. The arrows in columns A and C indicate the action potentials of C fibers and delta fibers, respectively.

radiation, but there was no alteration in the alpha and delta deflections shown on the lower channel.

The upper pair of action potentials in column B were recorded 19 minutes after those in column A, and they show recovery of a few C fibers. Twenty additional pulses of ultrasound at this time produced permanent blocking of all C fibers. Again there was no change in the alpha and delta deflections.

Between the records in columns B and C, 11 additional series of irradiations, comprising 400 pulses at increasing intensities and durations, were administered. The delta fiber deflection (arrow), recorded with a faster sweep in column C, was somewhat diminished by this irradiation. At this point 20 0.7-second pulses at a plate voltage of 800 were administered. The delta response was permanently abolished by this more intense irradiation, but the alpha response remained unchanged (5).

Between the records in columns C and D, 160 more pulses of still longer duration were administered without apparent effect on the alpha deflection. The reduction in alpha response seen in column D was produced by 60 0.8-second pulses at a plate voltage of 800.

As illustrated by this experiment, there is an inverse relationship between fiber size and vulnerability to ultrasound in mammalian peripheral nerves. It was, however, seldom as clear-cut as in Fig. 1. Although small fibers were most sensitive to irradiation in all experiments, the degree of differential block varied considerably, and the

ranges of dosage to which the different groups of fibers were sensitive often overlapped. Irradiation sufficiently intense to block C fibers usually affected conduction in some delta fibers as well. The alpha fibers were always most resistant. In general, the relationship between dosage and blocking was fairly linear throughout any one experiment, but the dosage levels required to produce equivalent effects in different experiments varied considerably. The inconsistencies were too large to be accounted for by biological variability. An explanation is being sought in further investigations of the physiological basis of ultrasonic blocking.

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3. The ultrasound (1.0 Mcy/sec) was generated piezoelectrically by excitation of a quartz crystal and focused with a polystyrene lens. It was transmitted through a saline-filled cone covered by a latex membrane into degassed mineral oil covering the nerve [See T. F. Hueter, H. T. Ballantine, Jr., W. C. Cotter, J. Acoust. Soc. Am. 28, 192 (1956)].

 The conduction speed of the fastest C fibers was found to be approximately 1 m/sec at 37°C.

5. The small deflection immediately following the alpha response in the lower records in Fig. 1 was caused by double firing of a few alpha fibers. It resulted from the intensity and duration of the stimulus required to excite the C fibers.

7 July 1961

#### Gonadotrophic Hormones Affect Aggressive Behavior in Starlings

Abstract. Injections of gonadotrophic hormones into subordinate male European starlings produced reversals in social rank, suggesting that pituitary gonadotrophic hormones rather than gonadal hormones influence aggressive behavior in this species.

The effects of gonadal hormones on the reproductive behavior of animals have been extensively studied (1). These hormones, androgens from the testes and estrogens from the ovaries, generally have proved to be very important in determining the characteristic behavior of each sex. Furthermore, the male hormone has long been recognized as a major determinant of aggressive behavior in animals (2).

In the European starling, Sturnus vulgaris, however, androgens apparently do not play a major role in determining aggressive behavior. Davis (3) found that castrated male starlings in the laboratory maintained song and fighting behavior for as long as a month after castration and, furthermore, that the social rank of individual starlings in the group was not affected by injections of testosterone. In addition, Hilton (4) and I (5) noted that there is a discrepancy between the yearly behavioral and gonadal cycles in male starlings. That is, both the weights of testes and the intensity of aggressive behavior reach a high point during the spring breeding season, and then decline during the summer. But aggressive behavior increases again in the fall even though gonadal weights remain at their minimal summer level. The apparent lack of relationship between androgen levels and aggressive behavior led to the investigation of behavioral effects of other hormones, and, as part of a more comprehensive study of pituitary activity in starlings, to an investigation of the effects of injected commercial gonadotrophins on aggressive behavior of caged male starlings, both intact and castrated

In the first series of experiments, groups of five or six birds were placed together in a large flight cage and left together until a clear-cut social rank was evident (about 1 week). Then the lowest-ranking members of the group were given daily injections (for about 2 weeks) of Armour mammalian luteinizing hormone (LH). Administration of this hormone sometimes resulted in increased aggressiveness in the subordinate birds, but rarely in any increase in social rank. It was postulated

that this failure to demonstrate behavioral changes might be attributed to learning; that is, once the social rank was established, the hormonal stimulus to change was not adequate to overcome the well-established, learned social rank. Consequently, the experimental procedure was redesigned in order to eliminate the effects of learning as much as possible.

In the new procedure, male birds, which had previously been kept in separate cages, were placed together in pairs in an observation cage just long enough to establish dominance of one over the other. The observation cage was a cubical box 3 feet square. It was lined with white oilcloth on three of its vertical sides; the fourth side was covered with hardware cloth so that. through a one-way mirror, the birds could be observed. The birds fought vigorously for the possession of the single perch. Control of this perch was the criterion of dominance. After dominance of one bird had been established (about 15 min), the subordinate bird was given LH and its behavior toward its cage partner was again observed (dominant birds were given saline injections). The first experiment was a pilot experiment to determine hormone dosages. Each pair consisted of a castrated male starling and an intact male bird, and, in five out of six pairs, the castrate was initially dominant. Reversals of dominance occurred in two cases upon injection of 250 µg and 900 μg of hormone, respectively. Bird 5, which was initially given 2000 µg of testosterone propionate, did not assume dominance after injection of either testosterone or luteinizing hormone. In the second experiment, castrated birds were initially dominant in 11 out of 12 pairs. When the subordinate birds were given 500 µg of LH, reversal of dominance occurred in six out of eight pairs. In the third experiment, every bird was successively paired with every other bird in the group. In this experiment, in contrast to the earlier experiments, the castrated birds were not always initially dominant. However, this experiment was done in March, when the pituitaries of intact birds show a high level of gonadotrophic activity (5). The results of these three experiments are summarized in Fig. 1.

In order to reduce the possible effects

of learning even more, a fourth experiment was conducted with birds which were not paired to establish dominance before hormone injections were administered. In this case, only intact male birds were used. One of the birds in each pair was given 1000 ug of LH, the other saline; they were then placed together in the observation cage. If LH had no behavioral effects, one would expect the hormone-injected bird to dominate in 50 percent of the pairs and the saline-injected bird to dominate in 50 percent of the pairs. However, the hormone-injected birds were observed to dominate in 81 percent of the pairs; out of 16 pairs, there were two pairs in which no fighting occurred at all and one pair in which the saline-injected bird dominated. In 13 out of 16 pairs (81 percent) the hormone-injected bird dominated.

These experiments indicate that commercial luteinizing hormone from mammalian sources, when administered in large doses, can influence the aggressive behavior of caged male starlings. It is also of interest to note the rapid effect of the injections of this hormone on the behavior of the birds. Reversals of dominance, if they occurred at all, generally occurred within the first 10 to 15 minutes after injection. This rapid reaction indicates that perhaps the circulating hormone acts directly on behavioral centers in the brain. In addition, the dominance of castrated birds over their intact cage-mates is noteworthy. If LH is a determinant of aggressive behavior in the starling, as it appears to be, the aggressiveness of castrated birds may be a result of higher gonadotrophic activity in the pituitaries of castrates. Various workers, including Kato (7), working with chickens, found that castration increased the gonadotrophic activity of the pituitary.

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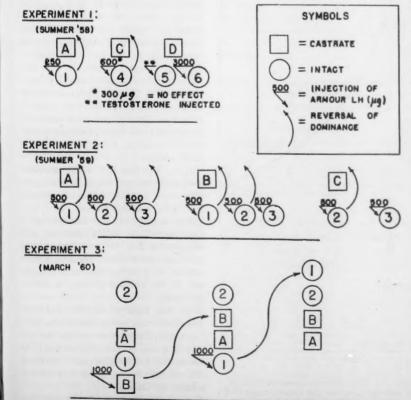


Fig. 1. Effects of hormone injections upon dominance of male starlings.

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## Localization of Carbonic Anhydrase in the Nervous System

Abstract. Single-cell analyses of carbonic anhydrase demonstrate that this enzyme is selectively concentrated in the glial and choroid cells of the rat brain. The nerve cells show a very low carbonic anhydrase activity. This specific localization supports the view that glial carbonic anhydrase is implicated in a mechanism for the active transport of chloride from the capillaries to the interstitial and cerebrospinal fluids.

Although the presence of carbonic anhydrase in the nervous system was demonstrated as early as 1943 (1) and has been studied in detail as far as gross distribution of the enzyme is concerned (2) no conclusive data have been reported about its fine localization. This is partially due to the lack of a reliable histochemical method for the demonstration of carbonic anhydrase in tissue sections (3). The de-

velopment of a sensitive micromethod based on a modification of the Cartesian diver technique of Linderstrøm-Lang (4), which allows determination of carbonic anhydrase in single tissue elements (5), offered the possibility not only of investigating this problem but also of providing new information on the functional relationship between glia and neurons.

Samples of single nerve cells and of the glia cells surrounding them (oligodendrocytes) were isolated under the microscope from fresh unstained preparations of the lateral vestibular nucleus of Deiters, according to the technique described elsewhere (6). Single-cell preparations of choroid plexus and erythrocytes were also studied. The hooded rat (Long-Evans) strain was used throughout.

Equivalent volumes of nerve and glial cells were dissected out (6), and their carbonic anhydrase activity was

measured separately by  $CO_2$  evolution, at 25°C, from NaHCO<sub>3</sub> (final concentration,  $1 \times 10^{-4} M$ ) in the presence of 0.1M sodium phosphate buffer at pH 7.5. The uncatalyzed reaction and the activity curves of different known concentrations of semipurified carbonic anhydrase preparations were determined for each experiment and compared with the curve obtained with the isolated cell preparation as shown in Fig. 1.

Control experiments carried out with either the semipurified samples of carbonic anhydrase or the cell preparations in the presence of acetazoleamide  $(6 \times 10^{-7}M)$  showed a complete inhibition of the enzyme activity.

The enzyme activity was determined and expressed in molar terms according to the method of Maren, Parcell, and Malik (7).

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The enzyme activity of a cell preparation which was found to be equivalent to the activity observed in a diver filled with the semipurified carbonic anhydrase solution (see Fig. 1) varied between 38 and 360  $\times$  10<sup>-18</sup>M (mean,  $99 \times 10^{-13} M$ ) in the glial cells, while in the corresponding nerve cells this activity was only 0.45 to  $5 \times 10^{-18} M$ (mean,  $1.95 \times 10^{-18}M$ ), the ratio between the glial- and the nerve-cell activity varying in a single preparation between 28 and 85 (16 experiments). Volumes varying between 18 and  $50 \times 10^{8} \mu^{8}$  of oligodendroglia (representing 7 to 20 glial cells) exhibited, therefore, concentrations of carbonic anhydrase (moles per unit volume) up to 120 times higher than concentrations in a single nerve cell of equivalent volume.

It is felt that the small carbonic anhydrase activity found in the nerve cells may be due to contamination with glial material.

The activity of the enzyme in a single intact red cell preparation was estimated as  $2 \times 10^{-90}$  mole; in a single nerve cell, as  $3 \times 10^{-90}$  mole; in a glial cell, as  $18 \times 10^{-90}$  mole; and in a single cell of the choroid plexus, as  $300 \times 10^{-90}$  mole.

On the basis of activity per unit volume it may be calculated that carbonic anhydrase activity in the red cell is 670 times, in the choroid cell 250 times, and in the glial cell 120 times the activity in the nerve cell of the nucleus of Deiters.

As it has been found (8) that the mass per unit volume of fresh glial

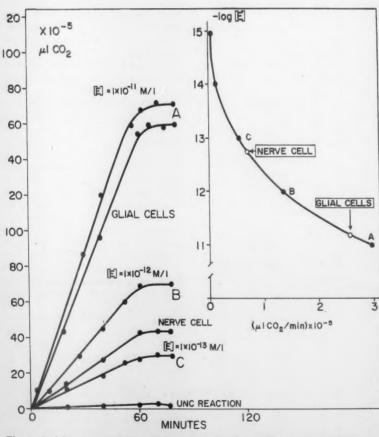


Fig. 1. Activity curves (A, B, and C, at left) for three different concentrations of a semipurified carbonic anhydrase preparation and the curve for the uncatalyzed (UNC) reaction. These are compared (insert) with the activity of a single nerve cell and an equivalent volume of glial cells.

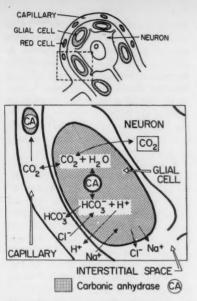


Fig. 2. (Top) The cellular localization of carbonic anhydrase in the central nervous system; (bottom) a proposed mechanism for the transport of chloride and sodium (see text),

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cells in the nucleus of Deiters is the same as that of the corresponding nerve cells (about 0.20  $\mu\mu g/\mu^3$ ), it is appropriate to make a direct comparison of equivalent volumes of glial and nerve cells.

Studies in which the inhibition of carbonic anhydrase altered the formation and the electrolyte composition of the cerebrospinal fluid implicate this enzyme in its production (9, 10). The principal change is represented by a decreased Cl- gradient in the cerebrospinal fluid (10); the active transport of Cl is indicated by its concentration in the cerebrospinal fluid against the electrochemical gradient (11). The demonstration of selective high localization of the enzyme in the glial elements of the central nervous system indicates the site where this process may be presumed to act. Figure 2 shows schematically the localization of carbonic anhydrase in the nervous tissue and a possible two-step mechanism for the transport of chloride (and eventually sodium), which can be summarized as follows.

1) Carbon dioxide, which has very recently been recognized (12) as the immediate product of the decarboxylation reactions in the brain, can rapidly diffuse inside the neuron and, from it, into the adjacent glial cells, where it

is rapidly hydrated to carbonic acid (HCO<sub>a</sub> at body pH) in the presence of carbonic anhydrase.

2) A selective exchange of chloride from the adjacent capillary into the glial cell and from there to the interstitial space and cerebrospinal fluid can then take place.

In this way the high intracellular HCOs rapidly made available from CO2 and H2O in the presence of carbonic anhydrase may be linked with the active transport of chloride into the interstitial space and cerebrospinal fluid.

This view represents a further extension of the concept of a secretory system (10) localized not only in the choroid plexus but also in the glial tissue. The very small and probably artifactitious amount of carbonic anhydrase found in the neuron may be regarded as evidence that the role of this enzyme in the central nervous system is secretory, as it is in most other sites.

It can finally be pointed out that in the structure studied (the nucleus of Deiters of the rat), the anatomical interrelationship of the glial cells to the neuron and to the capillaries (5) gives further support to the view that the glia has a strategic position (see Fig. 2, top) in the postulated secretion mechanism (13).

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  B-1297 from the National Institutes of
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- 22 June 1961

#### Ocular Lesions Produced by an Optical Maser (Laser)

Abstract. Ocular lesions have been experimentally produced in rabbit by a pulsed optical maser (laser). The high-energy density delivered in a single 0.5 msec pulse was sufficient to cause instantaneous thermal injury to the pigmented retina and iris of the brown rabbit. Ophthalmoscopically, the retinal lesions resembled flash burns from an atomic fireball.

It is well known that the visible and near-visible regions of the electromagnetic spectrum are capable of producing thermal injury to the eye (1). The retina is particularly vulnerable, since the energy focused upon its surface by the refracting media is readily absorbed by the pigmented layers of the retina and neighboring choroid (2). Chorioretinal burns from viewing a solar eclipse or the atomic fireball are typical of the lesions that may result (3, 4).

Recently, extension of molecular amplifier theory to shorter wavelengths has led to the development of optical masers, capable of generating coherent, essentially monochromatic radiation of high intensity (5). These devices, destined for use in communications, the medical sciences, and military installations, constitute another potential source of ocular injury due to accidental exposure.

From a consideration of the emission characteristics of a pulsed ruby maser and the transmission properties of the eye, estimates of the energy density at the retina indicate that the burn threshold may be greatly exceeded by exposing the eye to a single 0.5-msec burst (6). This report describes preliminary studies of retinal and iris lesions in rabbit produced by an optical maser.

A pulsed ruby maser (Vireo I laser developed by Technical Research Group) was employed. The ruby and its helical excitation source were enclosed in a cylindrical housing and mounted on an optical bench. Laser output was 0.1 joule/0.5-msec pulse, emitted in a coherent, monochromatic  $(\lambda = 694.3 \text{ m}_{\mu})$  beam, 1 cm in diameter. An adult, pigmented rabbit was held in a restraining box and placed on an adjustable mount with the eye approximately 30 cm from the emission face of the ruby. Pupils were maximally dilated with 2 percent Cyclogyl and 10 percent Neo-synephrine.

In rabbit, regions proximal to the optic nerve head contain medullated nerve fibers that form an elliptical area in which energy absorption is least efficient. When the beam impinged on this area the visible lesion was minimal, but vitreous bubbling was evident. The laser beam was, therefore, directed toward the inferior pigmented portions of the retina. Since ophthalmoscopic sighting was not incorporated into the apparatus for these preliminary trials, the accuracy of alignment could be ascertained only after exposure and subsequent examination of fundus alterations. With practice, however, the desired target site could be readily attained by visual approximation.

Figure 1A shows the ophthalmoscopic appearance of normal rabbit retina in a pigmented region inferior to the optic disk. The pigment is irregularly dispersed. Figure 1B shows the same area in the fellow eye after exposure to a single pulse of the laser beam. There is a relatively discrete, circularly shaped lesion about 3° in diameter. The lesion consisted of blanched, coagulated retina elevated in crater fashion and contained a small, centrally placed hemorrhage. Figure 1C is a photograph of the same lesion 5 days later. The appearance was that of a flat white scar with pigment clumping in and around the area. Figure 1D shows the immediate effects of exposure to three closely grouped successive pulses in another rabbit eye. The fundus changes, although more extensive, appear to be similar to those of Fig. 1B. Again, there were well-defined, elevated lesions. In addition, there was more pronounced pigment disruption, a larger area of blanched tissue, and a large hemorrhage extending into the vitreous. In general, the retinal lesions produced by the laser were profound and reminiscent of those occurring after exposure to atomic bomb explosions (4).

A second experiment was carried out with the pigmented iris of a brown rabbit as the biological target. Figure 1E shows the normal rabbit iris. The iris of the other eve was exposed to several pulses from the laser. The beam was converged by a short-focus lens and directed to various positions on the iris surface. The results are shown in Fig. 1F. Each arrow points to the lesion produced by a single laser pulse. In every instance the lesion was observed immediately after exposure and was characteristically a dark brown, irregularly shaped burn. When the eve was examined several days later, the pupil constricted in a grossly eccentric manner suggestive of internal damage to the iris.

The ocular abiotic effects described in this report were produced by a coherent source of intense field strength. As amplified light systems are developed and adapted to fulfill military, industrial, and medical objectives, it is essential that attending personnel be fully cognizant of this potential hazard. Investigations are currently in progress to determine threshold levels for the production of ocular lesions.

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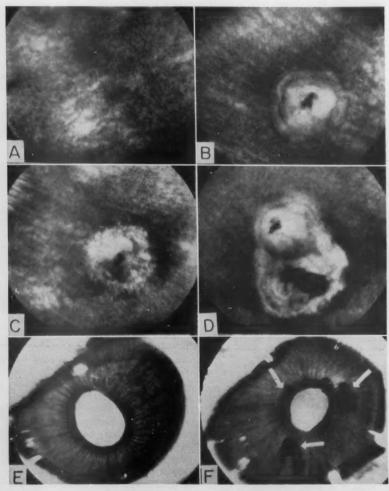


Fig. 1. Ocular burns produced by a laser beam. A, Fundus, showing a portion of normal, pigmented rabbit retina; B, lesion in the same area of the fellow eye following a single exposure to the laser; C, the lesion, 5 days later; D, lesions in another rabbit retina after three exposures to the laser beam; E, normal iris of a pigmented rabbit; F, iris burns produced by multiple exposures of a focused laser beam. Each arrow points to the lesion produced by a single exposure.

## Oral Proline Tolerance in Osteogenesis Imperfecta

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Abstract. Studies were carried out to test the hypothesis that a disturbance in proline or hydroxyproline metabolism, or both, is associated with defective collagen formation in osteogenesis imperfecta, a generalized disorder of connective tissue. Oral tolerance for proline in affected patients was lower than in comparable controls.

In 1952 Follis (1) emphasized morphological similarities of connective tissue in osteogenesis imperfecta and scurvy. He demonstrated in both disorders formation of argyrophilic and metachromatic fibers which are characteristic of reticulum or immature collagen, and he proposed that a similar defect exists in the collagenous portion of bone matrix in both conditions. Robertson et al. (2) and Gross (3) have shown deficient formation of collagen in the scorbutic guinea pig, and Gould and Woessner (4) have postulated a failure of hydroxylation of proline as a basic defect in scurvy. These observations have assumed more important proportions when considered in the light of recent observations by electron microscopy of hydroxyapatitecrystal formation and growth which appear to begin in apposition to collagen fibers in osteoid matrix (5).

Proline, a nonessential amino acid, can be formed from glutamic acid and ornithine, and proline-C14 can be found in Kreb's cycle intermediates soon after introduction into the body (6). Stetten (7) has shown that proline can be readily hydroxylated to form hydroxyproline in the rat, and she has shown also that this reaction is not reversible. Orally fed hydroxyproline is incorporated not at all or to a limited degree into mature collagen. It has been pointed out by a number of observers that hydroxyproline is found primarily in collagen and in no other structural proteins, and it has been proposed that an activated proline, probably proline adenylate, is formed prior to its incorporation into the collagen polypeptide and its subsequent hydroxylation

This study was undertaken to determine whether a rise in-serum hydroxyproline could be detected after oral administration of proline in patients with osteogenesis imperfecta and in suitable controls. Lack of hydroxylation of proline or lack of incorporation of either proline or hydroxyproline into

collagen might be expected to be reflected by abnormalities in the blood levels or urinary excretion of these amino acids. There is ample precedence for the belief that an enzymatic defect in the metabolism of a given substrate is reflected in abnormalities in the disappearance curve when the organism is subjected to a load of the substrate.

Serum levels of proline were determined for 8 hours after oral administration of proline (65 mg/kg of body weight) to seven children, ages 6 to 12 years, with osteogenesis imperfecta congenita (1) and tarda (6), and nine children, ages 6 to 12 years, who were normal (5) or had nonmetabolic orthopedic conditions (three cases of club feet and one case of mild cerebral palsy). All subjects had been on a regular diet and were fasted 12 hours overnight prior to and during the test. Proline was determined by a modification of the method of Troll and Lindsley (8). Hydroxyproline in the blood and urine was determined by a modification of the Wiss method (9).

Figure 1 demonstrates a difference in the averaged tolerance curve of the control group of children and the curves for affected children with osteogenesis imperfecta. A striking difference in the curves is noted especially in the first 2 hours of the tolerance test. Normal 95-percent confidence limits are shown on the curve of the control subjects for each blood specimen obtained. Three other patients with the congenita form of the disease have demonstrated low

oral tolerance curves for proline. Patients with the tarda form of the disease approached normal values. Urinary clearance of proline is within normal limits during the test [0.2 to 0.5 ml/min (10)]. Preliminary results indicate that free hydroxyproline blood levels rise two to three times the fasting level (2 to 6  $\mu$ g/ml) after oral administration of proline (65 mg/kg of body weight) to patients with osteogenesis imperfecta and control subjects.

It is apparent that no gross "diabetictype" proline tolerance curve has been demonstrated in osteogenesis imperfecta similar to that observed with phenylalanine in phenylketonuria. Instead, lower maximum values were uniformly demonstrated in patients with this disease than in suitable controls. This finding could be explained by a gastrointestinal absorptive defect or more rapid incorporation of proline into metabolic pathways in patients with osteogenesis imperfecta. Urinary loss was excluded. It would appear that an absorptive defect for proline is not the primary lesion in osteogenesis imperfecta since this factor alone would fail to explain the findings present at birth in the more severely affected children.

In the study of osteoporotic bone conditions, the investigator is still confronted with many unanswered questions. If osteoporosis is related to deficient collagen synthesis or synthesis of an abnormal collagen, how does this affect calcification, crystal aggregation, and growth? Whether low oral tolerance

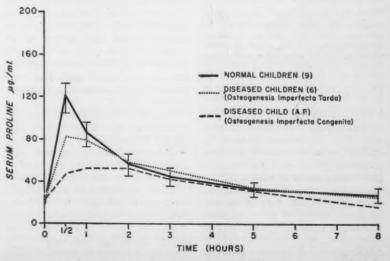


Fig. 1. Levels of proline in serum after oral administration of 65 mg of proline per kilogram of body weight.

for proline reflects a basic disorder in metabolism which significantly influences the formation of immature collagen in osteogenesis imperfecta cannot be answered from this study. A hydroxylating defect could not be demonstrated by the present techniques. It is noteworthy, however, that proline, one of the principal constituents of the polypeptide chain of collagen and also the precursor of hydroxyproline, should have a low tolerance curve when the amino acid is administered orally (11).

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16 June 1961

#### Longevity of Fusarium oxysporum in Soil Tube Culture

Abstract. In soil tube culture, representatives of three biologic forms of Fusarium oxysporum survived unchanged morphologically for 11 years or more. An isolate of the muskmelon wilt fungus remained viable after 17 years' storage in dry air at a temperature of from 3° 4°C. The surviving unit was found to be the chlamydospore.

The traditional method of maintaining fungus cultures by making transfers from them at frequent intervals to artificial media is laborious and timeconsuming and is not satisfactory for maintaining organisms unchanged for long periods of time. Other more or less dependable methods have come into use during the last 30 years, but some of them are applicable only to specific organisms.

Maintenance of fungus cultures in tubes of sterilized soil has found acceptance among some plant patholo-

gists. Miller et al. (1) showed that when the muskmelon wilt fungus Fusarium oxysporum f. melonis (L. and C.) Snyder and Hansen and other fusaria are maintained on agar, the "wild type" is rapidly displaced by mutants. He reported success in maintenance of the "wild type" and retention of viability of the melon pathogen after it had been cultured for 15 months in soil tubes. Gordon (2) affirmed the advisability of using soil culture as a means of preserving Fusarium species. Atkinson (3) found that representatives of six of 32 genera of fungi were viable after 5 years in dried soil culture. Members of F. oxysporum were found in the surviving group.

The study reported here was specifically concerned with an investigation of the longevity and the means of survival in soil culture of isolates of F. oxysporum causing wilt of three differ-

From 1946 until 1953, stock cultures of Fusarium oxysporum f. melonis were prepared, and from 1948 until 1953, cultures of F. oxysporum, f. lycopersici and f. niveum, the causal agents of wilt of tomato and watermelon, respectively. The following procedure was used. Test tubes of 25-cm<sup>8</sup> capacity were twothirds filled with sandy soil containing 10 percent of muck. The mixture was saturated with water, and the tubes were plugged and autoclaved. The fungi were single-spored, after 3 days' growth, from platings of infected plant tissue on 2-percent potato dextrose agar. When monosporous cultures were 3 or 4 days old, a small weft of mycelium from the periphery of the colony was transferred to the soil tubes. The resultant cultures were allowed to incubate in the laboratory at room temperature in a diffuse diurnal light for from 2 to 4 weeks before they were transferred to a refrigerator for storage at from 3° to 4°C.

Recently, the viability of many of the stock cultures was determined by plating soil suspensions (0.01 to 0.04 g) on a modified Martin's peptone agar medium, as described by Snyder et al. (4). The results are given in Table 1.

Table 1 shows that the three biologic forms of the soil-borne, wilt-producing fungi showed varying capacity for survival. One isolate from muskmelon showed exceedingly high survival after 13 years, and another, appreciable survival after 17 years. A few cultures contained no viable units. Some cultures were found to be contaminated with bacteria. The presence of the latter, however, did not appear to be the reason for nonsurvival of the fungus, because several bacterial-contaminated cultures showed high viability of the pathogen after 13 years.

Microscopic examination of culture plates inoculated with soil suspensions revealed that the fungus was surviving as chlamydospores. These findings are in agreement with those of Warcup (5) and Nash et al. (6), who isolated other species of Fusarium directly from the soil and found the surviving unit to be a chlamydospore.

In general, chlamydospores are spherical, varying in diameter from 9 to 14  $\mu$  (average, 12.6  $\mu$ ). The wall of the chlamydospore varies from smooth to slightly warty. Chlamydospores are found to contain from one to three oil globules. The chlamydospores occur singly and are usually firmly embedded in particles of organic matter, and often it is necessary to crush the particles before plating to determine the characteristics of the chlamydospore. On germination, chlamydospores have been observed to produce a single germ tube.

Growth of chlamydospores on various culture media showed that isolates of the three biologic forms of Fusarium oxysporum survived the long storage periods morphologically unchanged. Furthermore, comparative tests with fresh isolates showed that stored cultures of these three fungi survived without loss of pathogenicity.

Table 1. Survival of Fusarium oxysporum

Isolate	Number of years in storage	Number of surviving units per gram of soil
F.	oxysporum f.	melonis
Miller*	17	200
McKeen	15	1,200
Waters	13	3,300
Waters	13	134,000
Robinson	121/2	7,400
Quick	121/2"	4,400
Wigle	121/2	200
Setterington	121/2	74,000
Murray	8	32,000 .
Larabee	8	300
F.	oxysporum f. ly	copersici
Miller*	17	0
McKeen	12	95,600
Tecumseh	10	9,000
F	. oxysporum f.	niveum
Waters	11	33,000
Tingen	11	22,000

These cultures were prepared by J. J. Miller at the Harrow Laboratory in 1944. at the Harrow Laboratory

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The results of this study (7) not only demonstrate the usefulness of a long-term preservative method of maintaining biologic forms and races of F. oxysporum but indicate that maintenance of the fungi as the original "wild type" is due to survival as a dormant propagule.

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   This report is contribution No. 28, Research Station, Research Branch, Canada Department of Agriculture, Harrow, Ontario.

12 July 1961

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#### Photoperiodic Response of an Albino Mutant of Einkorn Wheat in Aseptic Culture

Abstract. An albino mutant of einkorn wheat which lacks plastid pigments was cultured in a test tube on nutrient agar medium containing 8 percent sucrose, under long and short photoperiods. The plants showed typical photoperiodic responses to long and short days, suggesting the presence of a pigment system, other than plastid pigments, which is sensitive to dim radiation.

In studies of photomorphogenesis, it would be desirable to separate the individual pigments or pigment systems from the whole-light-absorbing pigments in the tissues or organs concerned, since each pigment is expected to have a different function in the process of photomorphogenesis. Thus, albino or abnormally colored plants which lack some of the pigments as a result of spontaneous or artificial mutations may serve as useful experimental materials. Under field conditions, however, it is difficult to sustain the growth of albino plants until flower initials are formed. I succeeded in growing spring wheat to flower initiation in total darkness on nutrient agar media in test tubes (see 1).

The experiment reported here was conducted to test the response of the albino plants of einkorn wheat to long and short photoperiods by means of aseptic culture in test tubes.

The material used was an x-rayinduced mutant strain of einkorn wheat (2). In germination, the strain segregates normal green and albino seedlings in the ratio of 3 to 1. The plastid pigments of seedling leaves were analyzed according to the method of Koski and Smith (3). Neither chlorophylls nor carotenoids were found under the experimental conditions described elsewhere (4) (Fig. 1).

The culture medium, which contained modified White's minerals (1), 8 percent sucrose, 1 percent dried brewer's yeast in suspension, and 0.8 percent agar, was poured into test tubes (180 by 18 mm) in the amount of about 10 ml per tube. All the test tubes were then autoclaved at 1.2 kg above atmospheric pressure for 15 minutes.

The photoperiodic treatments were given by automatic artificial illumination from 20-watt fluorescent daylight tubes and a 40-watt incandescent lamp. The luminosity at plant level was about 1200 lux in 8 hours for a short day. For a long day, the illumination was supplemented to the extent of about 100 lux by using the incandescent lamp only for the remaining 16 hours.

The plants were grown at a temperature of 25 ± 2°C for 8 hours at the higher intensity and at a temperature of 20 ± 2°C for the 16 hours of lowerintensity illumination.

The seeds heterozygous for albino were sterilized with 10-percent chlorinated lime for 30 minutes and washed with sterilized distilled water. Then they were placed on the nutrient agar medium in the test tubes. About 10 days after sowing, the germinated albino and green segregants, which were kept at 25 ± 2°C in light, were steeped in the agar medium in order to have a better chance of absorbing the nutrients through the leaf surface.

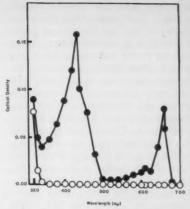


Fig. 1. Absorption spectra of ether extracts from leaves of normal green (solid circles) and albino (open circles) seedlings grown

All the plants were then subjected to the photoperiodic and temperature conditions mentioned above. Observation was made on days 67 and 107 after germination.

Table 1 shows that the albino plants, which are free of the plastid pigments, respond to the photoperiods just as the normal green plants do. Albino plants subjected to the long-day treatment produced flower primordia, and flower initiation was inhibited by the short day.

The sensitivity to light of the albino plant is, however, somewhat less than that of the normal green plant. The number of leaves formed on the main axis prior to flower initiation, which is generally considered a criterion of flowering response, is significantly greater in the albino plants than in green plants under the inductive long photo-

The net accumulation of dry matter in the shoot is greater under the long photoperiod than under the short day

Table 1. Cultures of normal green and of albino wheat plants in test tubes under long- and short-day

photope	11005.						
Type observe (No.)		Plants with flower initials (%)	Leaves formed on main axis (No.)	Length of stems (mm)	Flowering stages*	Dry wt of shoots (mg	
			Long days (	N, 67)			
Green	16	100	$7.94 \pm 0.17$	$128.6 \pm 6.0$	$3.1 \pm 0.1$	43.1 = 3.1	
Albino	16	100	$8.63 \pm 0.12$	$45.1 \pm 8.0$	$3.0 \pm 0.2$	$41.3 \pm 2.2$	
			Short days	N, 67)			
Green	. 12	0	$> 8.33 \pm 0.19$	†	0	$31.9 \pm 1.7$	
Albino	12	0	$> 8.80 \pm 0.29$	Ť	0	31.6 ± 1.9	
			Short days (	N, 107)			
Green	7	0	$>11.00 \pm 0.57$	+	0	73.3 = 10.1	
Albino	11	0	>12.09 = 0.30	†	0	$54.8 \pm 5.9$	

<sup>\*</sup> The stage was arbitrarily assigned, from 0 to 5, to correspond to the completely vegetative state and † All plants were rosetted, and stem elongation heading, respectively (6).

in both the green and the albino plants.

These results suggest that the albino plants as well as the normal green plants have a pigment system, other than the plastid pigments, which is sensitive to photoperiodic dim light. This pigment system has, as the results indicate, some effects on the promotion of growth and development by the long photoperiod in both the albino and the green plants. Promotion of the growth of fern gametophyte on sucrose medium by dim or red light of low dosages was reported and related to the nonphotosynthetic light requirement or the redfar-red absorbing system in the photomorphogenesis of plants (5). The plastid pigments, chlorophylls and carotenoids, do not seem to have a leading role in photoperiodism in wheat and, presumably, in many other plants (6). They would seem to favor, however, the flowering response through the production of some metabolites or the reaction of photosynthesis in high light intensity.

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#### Genetical and Geographic **Studies on Isoniazid Inactivation**

Abstract. Rapid and slow inactivators of isoniazid are homozygotes, and intermediate inactivators are heterozygotes. There is no dominance between the two alleles. The chasm between Eskimos and Caucasians in isoniazid metabolism is bridged by our investigation of the races

In 1956 we succeeded in measuring the biologically active plasma concentration of isoniazid with the simple and convenient vertical diffusion method (1, 2). Since then we have studied the inactivation of isoniazid in the blood of more than 3000 healthy and tuberculous persons and have found that the frequency distribution curve is trimodal.

Table 1. Population genetical data.

	No.	No. of inactivators					Frequencies of alleles			Test for random mating		
Races and districts	of sub-	Rapid		Intermediate		Slow		"Rapid"	"Slow"	σ		
	jects	No.	%	No.	%	No.	%	Kapiu	Slow	ø	$\chi^2$	(d.f. = 1)
Japanese*												
Hokkaido	122	53	43.5	58	47.5	11	9.0	0.6721	0.3279	0.0425	0.755	30-40%
Tohoku	94	55	58.5	32	34.0	7	7.5	0.7553	0.2447	0.0443	0.587	40-50
Shin-etsu	40	20	50.0	17	42.5	3	7.5	0.7125	0.2875	0.0716	0.056	80-90
Hokuriku	26	14	53.8	10	38.5	2	7.7	0.7308	0.2692	0.0870	0.013	80-90
Tokyo	166	79	47.6	71	42.8	16	9.6	0.6898	0.3102	0.0359	0.000	<95
Kanto	217	88	40.6	103	47.4	26	12.0	0.6429	0.3571	0.0325	0.246	60-70
Tokai	126	48	38.1	64	50.8	14	11.1	0.6349	0.3651	0.0429	1.152	20-30
Kansai	165	62	37.5	80	48.5	23	14.0	0.6182	0.3818	0.0378	0.121	70-80
San-in	89	36	40.4	39	43.8	14	15.8	0.6236	0.3764	0.0514	0.394	50-60
San-yo	90	30	33.3	47	52.2	13	14.5	0.5944	0.4056	0.0518	0.621	40-50
Shikoku	312	146	46.8	133	42.6	33	10.6	0.6811	0.3189	0.0263	0.109	70-80
Kyushu (N)	109	55	50.4	44	40.4	10	9.2	0.7064	0.2936	0.0436	0.039	80-90
Kyushu (S)	252	112	44.4	105	41.7	35	13.9	0.6528	0.3472	0.0300	1.645	10-30
Total for												
Japanese	1808	798	44.1	803	44.4	207	11.5	0.6634	0.3366	0.0111	0.054	80-90
Ainu	86	44	51.2	31	36.0	11	12.8	0.6918	0.3082	0.0498	2.055	10-20
Korean	65	. 29	44.6	29	44.6	7	10.8	0.6692	0.3308	0.0584	0.004	<90
Ryukyuan	124	42	33.9	64	51.6	18	14.5	0.5968	0.4032	0.0436	0.650	40-50
Thai	108	21	19.5	57	52.8	30	27.8	0.4583	0.5417	0.0478	2.455	10-20

<sup>\*</sup> In order from north to south.

The concentration of isoniazid was determined 6 hours after oral administration of 4 mg of isoniazid per kilogram of body weight. We classified the subjects as rapid inactivators if the concentration was equal to or less than 0.15 µg/ml; intermediate if the concentration was between 0.15 and 0.8; and slow if the concentration was equal to or greater than 0.8 (3). We may round off 0.15 to 0.2, but in this case the concentration less than 0.2 is rapid and that equal to 0.2 is intermediate. Our family study shows that rapid and slow inactivators are homozygous, that intermediate inactivators are heterozygous, and that inactivation of isoniazid is a character that is inherited without dominance.

We studied the patterns of isoniazid metabolism of several races in the Far East and found that the more southerly the region the higher the frequencies of "slow" alleles, obtained by the maximum likelihood method (Table 1). The chasm between Eskimos (4) and Caucasians is bridged by Ainus, Koreans, Japanese, Ryukyuans, and Thai. If we rearrange the experimental results reported by Mitchell et al. (5), Knight et al. (6) and Levy et al. (7) on the basis of our criterion, the incidences of "slow" characters in Americans are 44.5, 45.6, and 54.5 percent and those of "rapid" are 26.8, 17.0, and 9 percent, respectively. It is noteworthy that there is a rather wide zone of intermediate inactivation also in the whites.

There are local differences in the frequencies of "slow" and "rapid" alleles in Japan and, as in the case of racial differences, frequencies of "slow" alleles increase in more southerly districts, except Shikoku and Kyushu. Hokkaido also forms an exception to the north-south pattern. Because Hokkaido was recently developed and almost all its inhabitants are immigrants from various other districts in Japan. it is natural that the frequency of the alleles in this district is nearly equal to the mean value for all Japanese. The reason Shikoku and Kyushu, which are the two most southern islands in Japan, show rather low frequencies in "slow" alleles is unknown.

Since the frequencies of both alleles are relatively high, it might be presumed that pressure of selection on the alleles is weak. Accordingly, if our genetic hypothesis is valid, Hardy-Weinberg's law might hold for all the local groups indicated in the table. The test for random mating establishes that the observed and expected values agree remarkably well. Our hypothesis that rapid and slow inactivators are homozygotes, that intermediate inactivators are heterozygotes, and that there is no dominance between alleles is, we believe, amply proved by the population genetical analysis.

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#### Preference for Clear versus Distorted Viewing in the Chimpanzee

Abstract, Young chimpanzees preferred to look through a clear window rather than through a window that produced a distorted image of viewed objects. Performance did not appear to be affected by familiarity with the viewing stimulus.

The tendencies to look, to manipulate, and to remain alert and on the move appear very early in life, and much of the daily activity of a primate consists of responses which keep the animal in touch with what is going on in the environment. Thus, for example, rhesus monkeys will work persistently to look out of an enclosed cage and see objects (1). The purpose of the experiment reported here was to determine whether chimpanzees, in addition to being motivated to look at objects, also prefer a clear to a distorted view of an object. Such a preference would be expected by Woodworth, who states, "the seeking of clear vision is built into the individual organism. It is an immediate drive of great potency without regard to any ulterior motivation. . . . All the visual mechanism [of clear vision] requires for its activation is the presence of visible objects. ... What we said ... in defense of an exploratory drive is pertinent here, for perception is evidently the core of exploration. The direct goal of exploration is to find or perceive 'what is there' "(2):

Four chimpanzees approximately 21/2 years old (No. 188, Jenda; No. 173, Falweb; No. 175, Peck; No. 194, Saki) were given 28 5-minute trials, which were spaced over 7 days of testing. On each trial the subject was given access to two plastic windows (1½ by 2½ inches) mounted with their centers 12 inches apart in a wall of the home cage.

One window afforded a normally clear view, but in the other the plastic was bent so as to produce (for humans) sharp but distorted images of viewed objects. By sighting through the latter window from different orientations, variations in the degree and type of distortion could be produced, but in general the distortions were gross. Double images and elongation of the visual image in multiple dimensions were the most frequently occurring types of distortion

The positions of the clear and distorted windows were varied in balanced order from trial to trial. A seated human being, positioned 3 feet away from, and between, the two windows, served simultaneously as the viewing stimulus and as observer. By pressing a key he made a recording on a 2-channel operations recorder whenever the animal's face appeared in front of a window. To control for possible biases in response attributable to the presence of a particular person, two observers were used, a male and a female.

The amount of looking was scored from the recorder tapes by estimating the total number of marks representing 2 seconds spent by the subject in front of a window. By this criterion, the chimpanzees looked through one or the other of the windows about 30 percent of the total time; 65 percent of their looking was through the clear window. The clear window received higher scores than the distorted one on, respectively, 26 of 28, 22 of 26, 15 of 27, and 26 of 28 trials with the four animals (tied scores are excluded). For each animal except Peck (who had a position bias), p < .01 by sign test, and p < .05 by t test, with 3 degrees of freedom. "Testing" behavior-that is, moving rapidly back and forth before settling down for a time at the clear window-accounted for many of the responses to the distorted window.

It is unlikely that the viewing stimulus employed—a passive human beingproduced the preference for clear viewing solely because it was familiar to or had special significance for these chimpanzees. Two of the animals (Jenda and Falweb) were raised for the first 21 months of life under special conditions that severely restricted their environmental and social experience. At the time of this testing they had had a total of less than 100 hours of social experience, and their social behavior was in many respects deficient. However, they performed in essentially the same fash-

ion as did Peck and Saki, who were wild-born animals that had been in constant contact with other chimpanzees and with people since their arrival at the Yerkes Laboratories 11/2 years prior to this experiment (3).

In view of human interest in relatively simple forms of "incongruous" stimuli (4), it is conceivable that the chimpanzee's preference for clear viewing could be reversed under some conditions. Under the conditions of this experiment, however, Woodworth's position is supported. Butler's recent and closely related finding that rhesus monkeys look more at a projected image that is in focus than at an image that is out of focus (5) is further evidence for the primacy of clear vision.

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21 July 1961

#### Influence of Cage Type and Dietary Zinc Oxide upon **Molybdenum Toxicity**

Abstract. Molybdenum-fed rats housed in galvanized cages gained less weight and had lower hemoglobin levels than similarly fed rats housed in stainless steel cages. Since similar effects were produced in rats housed in stainless steel cages by increasing the zinc in their diets, it was concluded that zinc consumed by chewing on zinccoated cages was responsible for the abnormalities noted.

Ever since the early work of Ferguson (1) the toxicity of molybdenum has been widely studied (2-4). Many of these studies have utilized rats as the experimental animals (3, 4), and it is likely that, in many of the studies with rats, the type of cage in which the animals were housed was not considered important. The experiments reported here were initiated as a result of the observation that rats housed in galvanized (zinc dipped) cages suffered more

Table 1. Some effects of cage type and dietary zinc oxide upon molybdenum-fed rats. Abbreviations: SS. stainless steel: Gal, galvanized.

Lot	Addition to basal diet	Cage	6-wk wt. gain	Hemo- globin concen-	Concentration in dry liver (µg/g)		
No.		type	(g)	tration at 4 wk (g/100 ml)	Zn	Cu	Mo
	First experim	ent (average of	five rats p	er treatment)			
1		SS	135	12.2	70	18.6	0.9
2		Gal	132	12.0	95	10.0	1.0
2 3 4	200 ppm Mo	SS	62	12.5	65	25.0	21.0
4	200 ppm Mo	Gal	41	9.8	125	42.0	37.0
	Second experi	ment (average	of six rats	per treatment	)		
1'		SS	144	13.6	101	13.2	0.9
2'	0.05% ZnO	· SS	119	12.3	314	8.0	1.1
3'	0.10% ZnO	SS	104	10.9	370	7.7	1.2
4'	0.15% ZnO	SS	82	10.2	339	7.2	1.4
5'	200 ppm Mo	SS	48	14.7	95	43.7	31.6
1' 2' 3' 4' 5' 6' 7'	200 ppm Mo + 0.05% Znd		25	12.7	145	51.4	52.2
7'	200 ppm Mo + 0.10% Znd		16	12.0	233	50.9	47.1
8'	200 ppm Mo + 0.15% Znd		16	12.1	296	45.7	48.1

from molybdenum toxicity than those housed in stainless steel cages.

The weanling rats used in these studies (Sprague-Dawley strain males) were individually housed in cages with either stainless steel or galvanized wire floors and were provided food and tap water ad libitum. The basal diet was essentially the same as one described elsewhere (3) and contained (in percent): sucrose 81.5, vitamin-free casein (Nutritional Biochemicals) 10.0, Wesson oil 5.0, mineral mixture 2.5, and vitamin mixture 1.0. Copper at the level of 1.6 parts per million (ppm) was added as copper sulfate to bring the total copper, as analyzed, to approximately 2.5 ppm. The zinc content of the basal diet was approximately 8 ppm. Hemoglobin was determined by the acid hematin method with blood obtained from the tip of the tail. After the rats were fed the experimental diets for 6 weeks, they were killed and the livers were removed and dried for analysis. Copper was determined by the carbamate method (5), molybdenum by the thiocyanate method (6), and zinc by the dithizone method (5).

In the first experiment (lots 1 to 4) the rats were housed in stainless steel or galvanized cages and were fed either 200 ppm molybdenum, added as sodium molybdate, or none at all, as indicated in Table 1. The galvanized cage environment resulted in a significant (t >t.05,8) reduction in blood hemoglobin concentration, a highly significant (t> t.01,8) reduction in weight gain, and a highly significant (t > t.01.8) increase in concentrations of molybdenum

and copper in the livers of the animals fed molybdenum, when comparison is made with animals receiving molybdenum but housed in stainless steel cages (lot 3 compared to lot 4). The zinc level in the livers of the rats fed molybdenum and housed in galvanized cages was approximately twice the level in the livers of those fed molybdenum and housed in stainless steel cages. This difference may not be real, however, because of variability within treatments.

In the second experiment (lots 1' to 8') the rats were housed in stainless steel cages, and three different levels of zinc oxide and one level of molybdenum were added to the basal diet of the seven treatment groups as indicated in Table 1. The rats fed 0.05 percent zinc oxide had a weight gain of 83 percent of the controls, while those fed 200 ppm molybdenum and 0.05 percent zinc oxide had a weight gain of only 52 percent of the molybdenum-fed rats. Statistical analysis showed there was a significant interaction between the molybdenum and zinc oxide treatments when measured by weight gain (F >F.05,3,39). This would substantiate the report that there is an interaction between molybdenum and zinc (7). However, statistical analysis further showed there was no significant interaction between molybdenum and zinc oxide upon hemoglobin levels or copper concentration in the liver. That dietary zinc at a relatively low level (0.75 percent) is toxic has been established (8). In addition, G. Matrone (9) has indicated that zinc at the level of 0.05 percent in the diet was toxic for the rat.

The lowest level of zinc oxide fed with the molybdenum in the second experiment (0.05 percent) probably furnished more zinc oxide than the molybdenum-fed rats in the first experiment obtained from chewing on the galvanized cages. Food consumption records indicated that the rats in lot 6' consumed approximately 6 g of food per day (between the 3rd and 5th weeks) which provided a daily zinc oxide intake of approximately 3 mg. Although it is conceivable that a rat could obtain this amount of zinc oxide by chewing on a galvanized cage, it is unlikely that as much as 3 mg/day was consumed by the animals housed in zinc-coated cages during the first experiment, since their growth was more rapid than the growth of the animals in the second experiment, which were fed the same diets, plus zinc oxide, but were housed in stainless steel cages. Although the possibility remains that the increased toxicity of molybdenum was due to the presence of some contaminant other than zinc on commercially produced galvanized metal cages, it appeared that the zinc from the galvanized cages was responsible for this effect.

It is evident then that in the future when molybdenum, copper, or zinc studies are being conducted with animals in cages, the type of cage used should always be considered, as has been noted when other trace minerals were studied; perhaps some earlier experiments should be reevaluated in this light (10).

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- 29 May 1961



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Glen Canyon dam: diversion tunnel, left; construction site, right. [U.S. Bureau of Reclamation, by A. E. Turner]

## 128th Annual Meeting

There's still gold in Colorado's "shining mountains," but it's a kind of wealth the '59ers did not dream of. It took a scientist, indifferent to the lure of placer gold, to discern the source of Western economic growth. John Wesley Powell boated down the wild Colorado in 1869 and lived to spend the rest of his life reminding the nation that not gold or land but water is the real wealth of the West.

Water, land, and climate are major themes of the AAAS annual meeting in Denver in December. The interdisciplinary symposium in the social sciences, Water and Climate, convenes Thursday morning, 28 December, as one of the AAAS general sessions. Among other subjects, the symposium will take a look at the figures on whether cloud seeding has increased average rainfall, whether rainfall is related to meteor showers, and what the prospects are for hurricane control and man-made weather over large areas. Water Improvement, a general session symposium on Saturday, 30 December, will cover such subjects as electrochemical demineralization of water and new dimensions in pollution research.

The Colorado River's Upper Basin is a giant laboratory backdrop for the symposium on Land and Water Use cosponsored by the Agriculture and Geology sections (27, 28, 29 December). Here, in the last U.S. wilderness, high scalers are blasting the red-rock canyon walls and contractors are pouring concrete for three great Bureau of Reclamation dams. Glen Canvon dam (photo, right) will add 3.6 billion kilowatt hours annually to the West's great wealth of low-cost hydroelectric power. With Flaming Gorge and Navajo dams, Glen Canyon will store water of the fluctuating Colorado for Upper Basin states and may help ease such clashes as Arizona vs. California, a bitter water dispute that has been before the Supreme Court since 1952 and brought the Arizona National Guard out in 1935 to halt construction of the Los Angeles aqueduct. The new Glen Canyon bridge, highest steel arch bridge in the U.S., is now a link in U.S. highway 89. Underneath, the "old red bull" churns through two half-mile diversion tunnels blasted through each side of the canyon (photo, left.)

You are likely to hear a good deal at the land and water symposium about what these dams will mean for industrial development in a wilderness that holds 90 percent of U.S. uranium deposits and 200 other minerals, for the poverty-stricken Navajos, and for the competing uses of western land. The reporters include W. I. Palmer, assistant commissioner, U.S. Bureau of Reclamation, and L. B. Leopold, chief hydraulic engineer, U.S. Geological Survey.

You may also hear something about how Denver is dropping a tunnel into the heart of a mountain to bring 14 billion gallons of Blue River water each day to its faucets, and about the plan to tunnel under the Continental Divide to bring water from Frying Pan and Roaring Fork rivers on the western slope to the dry Arkansas valley in eastern Colorado.



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### **Program Summary**

Geology and Geography

Tuesday 26 December

**Ground Water Problems in the Rocky** Mountains and Great Plains District, Part I. Joint symposium of AAAS Section E-Geology and Geography and the Geological Society of America, cosponsored by the American Geophysical Union. Arranged by Theodore R. Walker. University of Colorado, William G. Weist, Jr., U.S. Geological Survey, Denver, will preside. Ground water in Colorado-its importance during a national emergency, Paul T. Voegeli, Sr. How much do we know about ground water in the Colorado High Plains?. Harold E. McGovern and Donald L. Coffin. Artesian aguifers of the Denver Basin, Colorado, George H. Chase, Legal and management problems related to the development of an artesian ground water reservoir. Edward A. Moulder. Engineering and geology as an aid in solving ground water litigation, Edward D. Jenkins.

Wednesday 27 December

General Session for Contributed Papers in Geology.

**Ground Water Problems in the Rocky** Mountains and Great Plains District. Part II. James H. Irwen, U.S. Geological Survey, Denver, will preside. Management of radioactive waste in a basalt terrane, Idaho, Raymond L. Nace. Geological aspects of the Rocky Mountain Arsenal disposal well, Louis J. Scopel. The measurement of geohydrologic features affecting waste movement at Hanford, Washington, Randall E. Brown and John R. Raymond. Artificial ground water recharge: an aid to better water management, Dean O. Gregg. Pond water for domestic use, R. W. Stallman. Hydrologic significance of six core holes in carbonate rocks, Nevada test site, Stuart L. Schoff and Isaac J. Winograd.

Section E Dinner. John M. Parker, Kirby Petroleum Company, Denver, arranger.

Retiring Vice President's Address, Section E. Richard J. Russell, director, Coastal Studies Institute, Louisiana State University, and vice president for Section E, will preside. Some attributes of numerical data in geology, William C. Krumbein, professor of geology, Northwestern University, retiring vice president for Section E.

Thursday 28 December
Section E Committee Meeting.

Association of American Geographers, Great Plains-Rocky Mountain Division

Program chairman: M. John Loeffler, University of Colorado.

Tuesday 26 December

Contributed and Invited Papers in Geography, I. Program of the Association of American Geographers, Great Plains-Rocky Mountain Division, cosponsored by Section E. Arranged by Karl Stacev, Kansas State University, Alan D. Tweedie, Newcastle University College, New South Wales, Australia, and University of Colorado, will preside. Cascade Alp slopes and Gipfelfluren as clima-geomorphic phenomena, Will F. Thompson. Agricultural frontier in northern Alberta: a preliminary look, Thomas M. Griffiths and Clark N. Crain. The proportional relief landform map, Merrill K. Ridd. Water balance and the history of ancient Lake Bonneville, Vasyl M. Gvodetsky and H. Bowman Hawkes.

#### Wednesday 27 December

Contributed and Invited Papers in Geography, II. Arranged by M. John Loeffler and the department of geography. University of Colorado. Col. Joseph P. Hereford, U.S. Air Force Academy, Colorado Springs, will preside. Population growth in California: a problem in distribution, Howard F. Gregor. Population change, resource use, and income distribution, Calvin Patton Blair. Recognizing and meeting the map requirements of the population explosion in the western United States, John C. Sherman. Colorado oil shale: an undeveloped strategic resource, Harold A. Hoffmeister.

Contributed and Invited Papers in Geography, III. Arranged by M. John Loeffler and the department of geography, University of Colorado. John C. Sherman, department of geography, University of Washington, will preside. Modern Los Angeles, creature of the population explosion, Howard J. Nelson. The impact of an exploding population on a semideveloped state: the case of Arizona, Andrew W. Wilson. The changing pattern of population distribution in Texas, Stanley A. Argingast. Implications of land inventory

10

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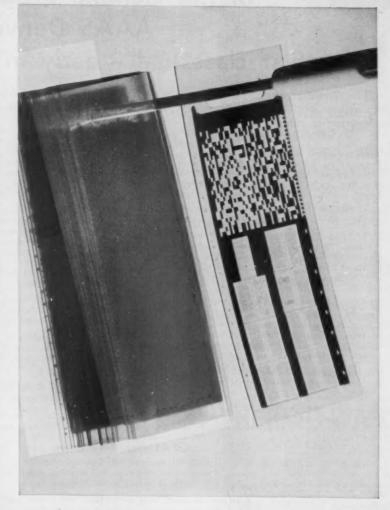
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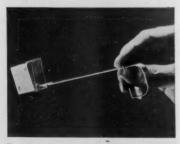
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#### **Program Content**

- 1. The two-session AAAS General Sessions, "Moving Frontiers of Science," Part I-Speakers: Howard A. Meverhoff and Arthur R. von Hippel; Harrison Brown, presiding. Part II-Speakers: Halton C. Arp and E. W. Fager; Harrison Brown, presiding.
- The 29th John Wesley Powell Memorial Lecture. Speaker: Glenn T. Seaborg; Paul M. Gross, presiding.
- 3. On "AAAS Day," the four broad, interdisciplinary symposia-Physics of the Upper Atmosphere; Geochemical Evolution-The First Five Billion Years; Existing Levels of Radioactivity in Man and His Environment; and Water and Climate-arranged by AAAS Sections
- 4. The Special Sessions: AAAS Presidential Address and Reception; Joint Address of Sigma Xi and Phi Beta Kappa by Harrison Brown; the Tau Beta Phi Address by John A. Logan; National Geographic Society Illustrated Lecture; and the second George Sarton Memorial Lecture by Joseph Kaplan.
- 5. The programs of all 18 AAAS Sections (specialized symposia and contributed papers).
- 6. The programs of the national meetings of the American Astronomical Society, American Society of Crimi-nology, American Nature Study Society, American Society of Naturalists, American Society of Zoologists,

- Beta Beta Biological Society, Biometric Society (WNAR), National Association of Biology Teachers, Scientific Research Society of America, Society for General Systems Research, Society of Protozoologists, Society of Systematic Zoology, and the Society of the Sigma Xi.
- 7. The multi-sessioned special programs of the American Astronautical Society (Hugh L. Dryden as dinner speaker), American Physiological Society, American Psychiatric Association, Association of American Geographers, Ecological Society of America, National Science Teachers Association, National Speleological Society —and still others, a total of some 70 to 80 participating organizations.
- 8. The sessions of the Academy Conference, the Conference on Scientific Communication, and the Conference on Scientific Manpower.
- 9. The sessions of the AAAS Cooperative Committee on the Teaching of Science and Mathematics, of the AAAS Committee on Science in the Promotion of Human
- Titles of the latest foreign and domestic scientific films to be shown in the AAAS Science Theatre.
- 11. Exhibitors in the 1961 Annual Exposition of Science and Industry and descriptions of their exhibits.

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programs in Chile, Donald D. Mac-Phail.

Geographers' Dinner. Arranged by M. John Loeffler, University of Colo-

#### Thursday 28 December

Contributed and Invited Papers in Geography, IV. Arranged by M. John Loeffler and the department of geography, University of Colorado. Karl Stacey, Kansas State University, will preside. The impact of growing metropolitan areas on water resources planning, Robert S. Collins. The Piedmont: Colorado's expanding core, M. John Loeffler and Albert W. Smith. Area and people in political geography, Joseph Velinkonja. Water problems in eastern Australia, Alan D. Tweedie.

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#### National Geographic Society

#### Saturday 30 December

Annual Lecture and Color Film of the National Geographic Society. Margaret Mead, member AAAS board of directors, will preside. The sacred well of Chichén Itzá, Matthew W. Sterling, research associate, Smithsonian Institution; Committee for Research and Exploration, National Geographic Society.

#### National Speleological Society

Program chairman: Brother G. Nicholas, F.S.C., University of Notre Dame.

#### Friday 29 December

Speleogenesis. Program of the National Speleological Society, cosponsored by AAAS Section E-Geology and Geography, and the Geological Society of America. Opportunities for geological research in caves, William E. Davis. Speleogenesis in the Marble Mountain area, Colorado, Donald Davis. Geology and speleogenesis of Porcupine Cave, Utah, Jon Haman. Crystal wedging as

Program summaries for the chemistry and mathematics sections appeared in the 27 October issue of Science, and for the physics and astronomy sections, in the 3 November issue. Program summaries for other sections will appear in subsequent issues.

a factor in cavern breakdown, William B. White and Elizabeth L. White.

General Session. Brother G. Nicholas, presiding. Notes on Colorado cave insects, Robert Ayre. Origin and development of lava tubes, William R. Halliday. Recent progress in Montana speleology, Howard McDonald. Preview of 1962 Black Hills meeting of NSS, John Streich.

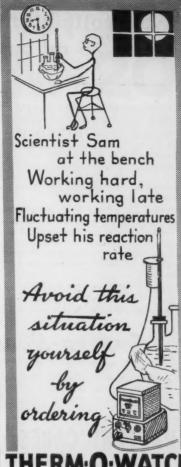
#### Agriculture

Land and Water Use with Special Reference to Mountain and Plains Regions. Symposium in four sessions, arranged by D. Wynne Thorne, Utah State University. One session jointly arranged by Terah L. Smiley, University of Arizona, and D. Wynne Thorne, Utah State University. Program of AAAS Section O-Agriculture, cosponsored by AAAS Section E-Geology and Geography, and the Committee on Desert and Arid Zones of the Southwestern and Rocky Mountain Division, and by the following societies: American Dairy Science Association, American Farm Economic Association, American Geophysical Union, American Society of Agricultural Engineers, American Society of Agronomy, American Society of Animal Production, American Society of Range Management, Ecological Society of America, Gamma Sigma Delta, Society of American Foresters, Soil Conservation Society of America, Wilderness Society, Wildlife Management Institute, Wildlife Society.

#### Wednesday 27 December

Part I: Land and Water Resources. Roland Renne, president, Montana State University, will preside. Population demands for land and water resources of the western hinterland, S. C. Smith. Land resources and potential use, R. D. Hockensmith, Water resources, development and uses, W. I. Palmer. Public grazing lands in the economy of the West, M. L. Upchurch.

Part II. Optimum Uses for Resources. E. F. Frolik, dean, College of Agriculture, University of Nebraska, will preside. Criteria and planning for optimum use, E. N. Castle. Economic priorities on water use in arid regions, Nathaniel Wollman. Agriculture as a competitive segment of multiple use, B. Delworth Gardner. Recreation as a competitive segment of multiple use, Marion Clawson.



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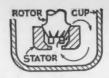
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Part III: Interdisciplinary Symposium in the Social Sciences: Water and Climate. Joint program of AAAS Section O-Agriculture and the Committee on Desert and Arid Zones Research of the AAAS Southwestern and Rocky Mountain Division, cosponsored by Sections E-Geology and Geography, K-Social and Economic Sciences, M-Engineering, and P-Industrial Science, the American Meteorological Society, and the American Geophysical Union. Arranged by Terah L. Smiley, University of Arizona, and Wynne Thorne, Utah State University. Terah L. Smiley will preside. A meteorologist looks at hydroclimatology, Paul R. Julian. Capture of additional water for increasing supplies, John W. Harshbarger. Weather modification, Earl G. Droessler. Legal aspects of a national water policy, Morris K. Udall.

#### Friday 29 December

Part IV: Impact of Public Policy on Land and Water Use. W. E. Morgan, president, Colorado State University, will preside. The government's responsibility for land and water, L. B. Leopold. Problems associated with wilderness and other reserves of public lands, C. R. Gutermuth. Problems growing out of the spaciousness of the West. M. M. Kelso. Public and/or private investment in resource development, W.

Part V: Projecting Management Programs. R. E. Hodgson, Director, Animal Husbandry Research Division, Agricultural Research Service, Beltsville, Maryland, will preside. Providing for multiple use in managing land and water, J. A. Hopkin. Modifying management and vegetation of watershed areas for improved water yields, F. H. Kennedy. Management associated with complex use for wildlife, livestock, and recreation, A. L. McComb. Managing private lands in relation to changing uses of public lands, N. Keith Roberts.

#### Saturday 30 December

Water Improvement, Part I. Symposium of the Committee on Desert and Arid Zones Research of the AAAS Southwestern and Rocky Mountain Division, cosponsored by AAAS Section O-Agriculture. Arranged by Terah L. Smiley, University of Arizona, and Joseph A. Schufle, New Mexico Institute of Mining and Technology. Terah L. Smiley will preside. Contamination of underground water-vicinity of Denver, William N. Gahr. New dimensions in water pollution research, Bernard B. Berger and Gordon McCullum. The salt water intrusion problems in coastal aquifers, David K. Todd. The zone of diffusion and its consequences, H. H. Cooper.

Water Improvement, Part II. John W. Harshbarger, University of Arizona, will preside. Electrochemical demineralization of water—theory and practice, George W. Murphy. Operating characteristics of ground water reservoirs occupying a trench, Robert E. Glover and Morris M. Skinner. Summary, Peter C. Duisberg.

#### Forthcoming Events

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#### November

16-19. American Anthropological Assoc., Philadelphia, Pa. (S. T. Boggs, 1530 P St., NW, Washington, D.C.)

23-25. Central Assoc. of Science and Mathematics Teachers, Chicago, Ill. (J. Kennedy, Indiana State Teachers College, Terre Haute)

Terre Haute)
24-25. American Soc. of Animal Production, Chicago, Ill. (C. E. Terrill, Animal Husbandry Research Div., U.S. Dept. of Agriculture, Beltsville, Md.)

24-25. Federation of American Scientists, natl. council, Chicago, Ill. (D. M. Singer, FAS, 1700 K St., NW, Washington 6)

24-25. National Council for Geographic Education, Philadelphia, Pa. (L. Kennamer, Dept. of Geography, Univ. of Texas, Austin)

25-26. American College of Chest Physicians, annual interim session, Denver, Colo. (M. Kornfeld, ACCP, 112 E. Chestnut St., Chicago 11, III.)

26. Medical Aspects of Sports, 3rd natl. conf., Denver, Colo. (F. V. Hein, AMA Committee on the Medical Aspects of Sports, 535 N. Dearborn St., Chicago, Ill.)

26-1. American Soc. of Mechanical Engineers, winter, New York, N.Y. (L. S. Dennegar, ASME, 29 W. 39 St., New York, N.Y.)

26-1. Radiological Soc. of North America, annual, Chicago, III. (R. P. Barden, 713 E. Genesee St., Syracuse 2, N.Y.)

27-28. Agricultural Meteorology, 4th conf., St. Louis, Mo. (K. C. Spengler, American Meteorological Soc., 45 Beacon St., Boston 8, Mass.)

27-29. American Soc. of Hematology, annual, Los Angeles, Calif. (J. W. Rebuck, ASH, Henry Ford Hospital, Detroit 2, Mich.)

27-29. Vehicle Systems Optimization Symp., Garden City, N.Y. (Meetings Dept., Inst. of the Aerospace Sciences, 2 E. 64 St., New York 21)

27-30. American Medical Assoc., Denver, Colo. (F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.)

27-30. American Soc. of Agronomy, jointly with Crop Soc. of America, Council on Fertilizer Application, and Soil Science Soc. of America, St. Louis, Mo.



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(ASA, 2702 Monroe St., Madison, Wis.) 27-30. Entomological Soc. of America, Miami, Fla. (R. H. Nelson, 4603 Calvert Rd., College Park, Md.)

29-I. Communication Wires and Cables, symp., Asbury Park, N.J. (H. Kingsley, U.S. Army Research and Development Laboratory, Fort Monmouth, N.J.)

29-1. Western Surgical Assoc., San Francisco, Calif. (W. W. Carroll, 700 N. Michigan Ave., Chicago 11, Ill.)

30. American Geographical Soc., New York, N.Y. (C. W. Bastable, Columbia Univ., New York 27)

30-1. Conference on Graduate Medical Education, Philadelphia, Pa. (P. Nemir, Jr., Dean, Graduate School of Medicine, Univ. of Pennsylvania, Philadelphia)

30-1. Vehicular Communications, Minneapolis, Minn. (J. Kahnke, Minneapolis-

Honeywell, Aero Div., 1541 Edgewater Ave., St. Paul 13, Minn.)

30-2. Purest Substances in Science and Technology, intern. symp., Dresden, Germany. (Sekretariat, Chemische Gesellschaft in der Deutschen Demokratischen Republik, Unter den Linden 68/70, Berlin W.8, Germany)

#### December

1. Symposium on Insulin, New York Diabetes Assoc., New York, N.Y. (New York Diabetes Assoc., 104 E. 40 St., New York 16)

1-2. Linguistic Circle of New York, 7th annual conf., New York, N.Y. (L. Urdang, Random House, Inc., 501 Madison Ave., New York 22)

2. International College of Surgeons,

intern. executive council, Chicago, Ill. (H. E. Turner, 1516 Lake Shore Dr., Chicago)

2. New York State Registry of Medical Technologists, annual seminar, New York, N.Y. (S. H. Keeling, 1719 Midland Ave., Syracuse, N.Y.)

2-7. American Acad. of Dermatology and Syphilology, annual, Chicago, Ill. (R. R. Kierland, Mayo Clinic, Rochester,

3-6. American Inst, of Chemical Engineers, New York, N.Y. (F. J. Van Antwerpen, AICE, 345 E. 47 St., New York 17)

4-6. Institute of the Aerospace Sciences, Aerospace Support and Operations, natl., Orlando, Fla. (R. J. Kotowski, 318 Virginia Dr., Melbourne, Fla.)

4-8. International Colloquium on Ionic Bombardment, Bellevue, France. (Natl. Scientific Research Center, 15 Quai Anatole France, Paris 7°, France)

4-9. Mathematics Instruction at Secondary and University Levels, Inter-American conf., Bogota, Colombia. (M. Alonso, Div. of Science Development, Pan American Union, Washington 6)

4-9. World Federation of Neurology, Problem Commission of Tropical Neurology, Buenos Aires, Argentina. (P. Bailey, Natl. Inst. of Neurological Diseases and Blindness, Bethedsa, Md.)

4-16. Inter-American Conf. on Education and Economic and Social Development, Santiago, Chile. (U.S. National Commission for UNESCO, Dept. of State, Washington 25)

4-16. Latin American Phytotechnical Meeting, 5th, Buenos Aires, Argentina. (U. C. Garcia, Organizing Committee, Rivadavia 1439, Buenos Aires)

5-7. Building Research Inst., Washington, D.C. (Scientific Liaison Office, Natl. Research Council, Sussex Dr., Ottawa, Canada)

6-7. UNESCO Intern. Non-Governmental Organizations on Extension of Intern. Collaboration in Education, Science and Culture to Africa, Paris France. (Place de Fontenoy, Paris 7°)

6-8. Conference on Document Copying by Photography, London, England. (A. J. O. Axford, Ozalid Co., Longston Rd., Loughton, Essex, England)

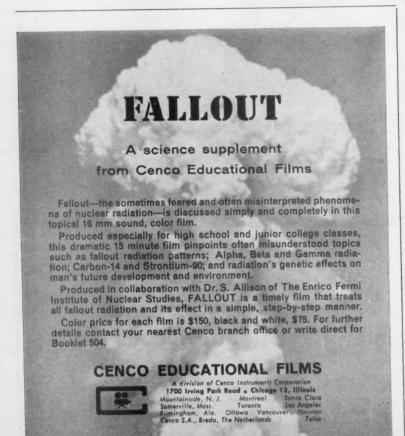
6-8. Electrical Furnace Steel Conf., 19th, American Inst. of Mining, Metallurgical and Petroleum Engineers, Pittsburgh, Pa. (Scientific Liaison Office, Natl. Research Council, Sussex Dr., Ottawa, Canada)

6-8. Latin-American Congr. of Pathological Anatomy, 3rd, Medellín, Colombia. (A. C. Henao, Laboratorio de Anatomía Patológica, Rua Botucatu 720, São Paulo, Brazil)

6-8. National Institutes of Health Symp. on Neuroendocrinology, Miami, Fla. (A V. Nalbandov, 102 Animal Genetics, Univ. of Illinois, Urbana)

6-12. American Acad. of Optometry, Chicago, Ill. (C. C. Koch, 1506-08 Foshay Tower, Minneapolis 2, Minn.)

6-16. Food and Agriculture Organization of the U.N. World Health Organization, Nutrition Conf. for the Far East, 5th, Hyderabad, India. (Intern. Agency Liaison Branch, Office of Director General, FAO, Viale delle Terme di Caracalla, Rome, Italy)











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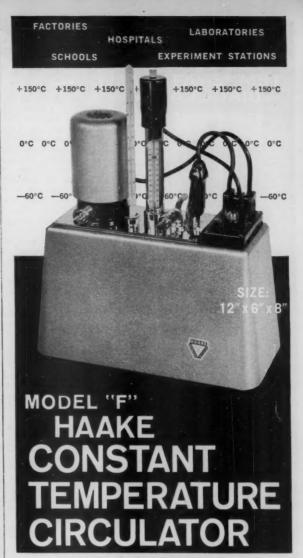
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6-16. Food and Agriculture Organization of the U.N., Far East Meeting on Production and Health, 3rd, Bangkok, Thailand. (Intern. Agency Liaison Branch, Office of Director General, FAO, Viale delle Terme di Caracalla, Rome, Italy)

7-8. Symposium on Sintered High-Tem-Oxidation-Resistant Materials, perature London, England. (S. C. Guilan, Powder Metallurgy Joint Group, Inst. of Metals,

17 Belgrave Sq., London)

7-9. American Chemical Soc. Southwest-Southeast regional meeting, New Orleans, La. (P. D. Accardo, California Chemical Co., Oronite Div., Belle Chasse, La)

7-9. New York Acad. of Sciences Conf. on the Cervix, New York, N.Y. (W. R. Lang, Jefferson Medical College, Philadel-

phia, Pa.)

7-9. Texas Acad. of Science, Galveston. (D. E. Edmondson, Mathematics Dept., 115 Bendect Hall, Univ. of Texas, Aus-

tin 12)

8. Food and Agriculture Organization of the U.N., Advisory Group on Training in Home Economics and Social Work, Rome, Italy. (Intern. Agency Liaison Branch, Office of Director General, FAO, Viale delle Terme di Caracalla, Rome)

8-9. American Rheumatism Assoc., interim session, Washington, D.C. (F. E. Demartini, 622 W. 168 St., New York 32)

8-9. Association for Research in Nervous and Mental Diseases, annual, New York, N.Y. (Scientific Liaison Office, Natl. Research Council, Sussex Dr., Ottawa, Canada)

8-9. Symposium on Plasma Membrane, New York, N.Y. (A. P. Fishman, New York Heart Assoc., 10 Columbus Circle, New York 19)

8-10. American Psychoanalytic Assoc., New York, N.Y. (D. Beres, 151 Central Park W., New York 23)

9-10. Academy of Psychoanalysis, New York, N.Y. (J. H. Merin, 125 E. 65 St.,

New York 21)

10-13. American Phytopathological Soc., Biloxi, Miss. (G. A. Zentmyer, Dept. of Plant Pathology, Univ. of California, Riverside)

10-14. Psychosomatic Medicine Symp., 6th, Philadelphia, Pa. (Miss M. R. Carmosin, Hahnemann Medical College and Hospital, 235 N. 15 St., Philadelphia 2,

10-17. Latin American Congr. on Microbiology, 2nd, San José, Costa Rica. (J. L. De Abate, Secretary General, Apartado 1404, San José)

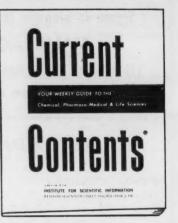
11. Society of Photographic Scientists and Engineers, Washington, D.C. (C. M. Bailey, Rte. 4, Box 404, Fairfax, Va.)

11-15. Agricultural and Public Health Aspects of Radioactive Contamination in Normal and Emergency Situations, technical seminar, The Hague, Netherlands. (Food and Agriculture Organization of the U.N., Intern. Agency Liaison Branch, Office of the Director General, Viale delle Terme di Caracalla, Rome, Italy)

11-15. Symposium on Organization of Agricultural Research, Muguga, Kenya. (Commission for Technical Cooperation in Africa South of the Sahara, Pvt. Mail Bag 2359, Lagos, Nigeria)

11-16. Ionospheric Soundings in the In-

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INSTITUTE FOR SCIENTIFIC INFORMATION 33 SOUTH SEVENTEEN STREET, PHILADELPHIA 3, PA. tern. Geophysical Year/Intern. Geophysical Cooperation-1959 Symp., Nice, France. (A. H. Shapley, URSI World-Wide Soundings Commission, Central Radio Propagation Laboratory, Natl. Bureau of Standards, Boulder, Colo.)

12-14. Association for Computing Machinery, eastern joint computer conf., Washington, D.C. (B. Oldfield, I.B.M. Corp., 326 E. Montgomery, Rockville, Md.)

12–15. American Soc. of Agricultural Engineers, Chicago, Ill. (J. L. Butt, ASAE, 420 Main St., St. Joseph, Mich.)

12-19. Latin American Congr. on Microbiology, 2nd, San Jose, Costa Rica. (J. de Abate, Apartado 1404, San Jose)

13. American Acad. of Arts and Sciences, Brookline, Mass. (J. L. Oncley, 280 Newton St., Brookline 46)

15-16. Oklahoma Acad. of Science, Stillwater. (D. Buck, Northern Oklahoma Junior College, Tonkawa)

17-18. International Congr. of Comparative Pathology, 9th, Paris, France. (L. Grollet, Comité International Permanent des Congrès de Pathologie Compareé, 63 Avenue de Villiers, Paris 17°)

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19-23. Inter-American Congr. of Psychology, 7th, Monterrey, Mexico. (G. M. Gilbert, Psychology Dept., Long Island Univ., Brooklyn 1, N.Y.)

22-29. Plant Tissue and Organ Culture, intern. symp., New Delhi, India. (P. Maheshwari, Univ. of Delhi, Delhi)

26-28. History of Science Soc., annual, Washington, D.C. (J. C. Greene, 1121 Iowa Ave., Ames, Iowa)

26-31. American Assoc. for the Advancement of Science, annual, Denver, Colo. (R. L. Taylor, AAAS, 1515 Massachusetts Ave., NW, Washington 5)

The following 35 meetings are being held in conjunction with the AAAS annual meeting.

AAAS Southwestern and Rocky Mountain Div., Committee on Desert and Arid Zones Research (M. G. Anderson, University Biological Station, Pulston, Mich.). 26-31 Dec.

Alpha Epsilon Delta (M. L. Moore, 7 Brookside Circle, Bronxville, N.Y.). 28 Dec.

American Assoc. of Clinical Chemists (R. L. Dryer, State Univ. of Iowa, Dept. of Biochemistry, Iowa City). 26–27 Dec. American Astronautical Soc. (J. Campbell III, R.C.A., Front and Cooper Sts., Bldg. 10-7, Camden, N.J.). 26–30 Dec.

American Astronomical Soc. (H. J. Smith, Yale Observatory, 135 Prospect St., New Haven, Conn.). 27–30 Dec.

American Economic Assoc. (J. W. Bell, Northwestern Univ., Evanston, Ill.). 26

American Educational Research Assoc. (G. T. Buswell, 1201 16 St., NW, Washington 6). 30 Dec.

American Meteorological Soc. (J. M. Austin, Dept. of Meteorology, Massachusetts Inst. of Technology, Cambridge 39). 26–31 Dec.

American Nature Study Soc. (B. Schultz, Dept. of Biology, Western Michigan Univ., Kalamazoo). 26-30 Dec.

American Physiological Soc. (R. G. Daggs, APS, 9650 Wisconsin Ave., Washington 14). 28 Dec.

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American Political Science Assoc., (E. M. Kirkpatrick, 1726 Massachusetts Ave., NW, Washington 6). 27 Dec.

American Psychiatric Assoc. (M. Ross, APA, 1700 18 St., NW, Washington 9).

27 Dec

American Soc. of Criminology (J. Chwast, New York Inst. of Criminology, 115-117 W. 42 St., New York 36). 29-30 Dec.

American Soc. of Naturalists (E. L. Green, Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine). 27 Dec.

American Soc. of Zoologists (C. B. Metz, Dept. of Oceanography, Florida State Univ., Tallahassee). 28-30 Dec.

American Sociological Assoc. (T. Parsons, Emerson Hall, Cambridge 38, Mass.). 28-29 Dec.

American Statistical Assoc. (D. C. Riley,

ASA, 1757 K St., NW, Washington 6). 29-30 Dec.

Association of American Geographers, Great Plains-Rocky Mountain Div., (M. F. Burrill, AAG, 1785 Massachusetts Ave., NW, Washington, D.C.). 29-30 Dec.

Beta Beta Beta Biological Soc. (F. G. Brooks, Box 515, Ansonia Station, New York 23). 27 Dec.

Colorado-Wyoming Acad. of Science (R. G. Beidleman, Zoology Dept., Colorado College, Colorado Springs).

Ecological Soc. of America (J. E. Cantlon, Dept. of Botany and Applied Pathology, Michigan State Univ., E. Lansing). 26-30 Dec.

Institute of Management Sciences (W. Smith, Inst. of Science and Technology, Univ. of Michigan, Ann Arbor). 29 Dec.

Mathematical Assoc. of America, Com-

mittee on Undergraduate Program in Mathematics (H. L. Alder, MAA, Univ. of California, Davis). 30 Dec.

National Assoc. of Biology Teachers (H. C. Kranzer, Temple Univ., Philadelphia 22, Pa.). 26-30 Dec.

National Assoc. for Research in Science Teaching (H. A. Branson, Dept. of Physics, Howard Univ., Washington 1). 26–30 Dec

National Assoc. of Science Writers (D. J. Dunham, Cleveland Press, Cleveland 14, Ohio).

National Science Teachers Assoc. (M. T. Ballou, Ball State Teachers College, Muncie, Ind.), 26–30 Dec.

National Speleological Soc. (D. N. Cournoyer, 2318 N. Kenmore St., Arlington 1, Va.). 29 Dec.

Scientific Research Soc. of America (D. B. Prentice, 51 Prospect St., New Haven, Conn.). 29 Dec.

Sigma Delta Epsilon (B. L. McLaughlin, 702 Butternut St., NW, Washington 12). 26–30 Dec.

12). 26–30 Dec.
Society of Protozoologists (N. D. Levine, College of Veterinary Medicine, Univ. of Illinois, Urbana). 27–30 Dec.

Society of the Sigma Xi (T. T. Holme, 51 Prospect St., Yale Univ., New Haven, Conn.). 29 Dec.

Society of Systematic Zoology (R. T. Abbott, Acad. of Natural Sciences, Philadelphia 3, Pa.). 27–30 Dec.

Tau Beta Pi Assoc. (R. H. Nagel, Univ. of Tennessee, Knoxville). 29 Dec.

United Chapters of Phi Beta Kappa (C. Billman, 1811 Q St., NW, Washington 9). 29 Dec.

27-29. American Economic Assoc., New York, N.Y. (J. W. Bell, AEA, Northwestern Univ., Evanston, Ill.)

27-29. American Folklore Soc., Cincinnati, Ohio. (T. P. Coffin, 110 Bennett Hall, Univ. of Pennsylvania, Philadelphia 4)

27-29. American Geophysical Union, 1st Western natl., Los Angeles, Calif. (A. N. Sayre, U.S. Geological Survey, Washington 25)

27-29. American Physical Soc., Los Angeles, Calif. (K. K. Darrow, 538 W. 120 St., New York 27)

27-29. Western Soc. of Naturalists, Eugene, Ore. (I. A. Abbott, Hopkins Marine Station, Pacific Grove, Calif.)
27-30. Institute of Mathematical Sta-

27-30. Institute of Mathematical Statistics, annual, New York, N.Y. (D. C. Riley, American Statistical Assoc., 1757 K St., NW, Washington 6)

28-29. American Chemical Soc., Div. of Industrial and Engineering Chemistry, Newark, Del. (Scientific Liaison Office, Natl. Research Council, Sussex Dr., Ottawa, Canada)

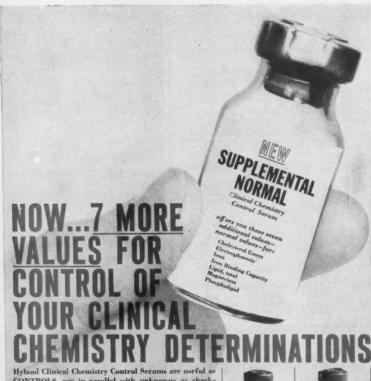
28-29. Linguistic Soc. of America, annual, Chicago, Ill. (A. A. Hill, Box 7790 University Station, Austin 12, Texas)

28-29. Northwest Scientific Assoc., Spokane, Wash. (E. J. Larrison, Univ. of Idaho, Moscow)

28-30. Archaeological Inst. of America, Detroit, Mich. (L. A. Campbell, 5 Washington Square N., New York 3)

28-30. Phi Delta Kappa, Bloomington, Ind. (R. S. Merkel, Indiana Central College, Indianapolis 27)

(See Issue of 20 October for comprehensive list)



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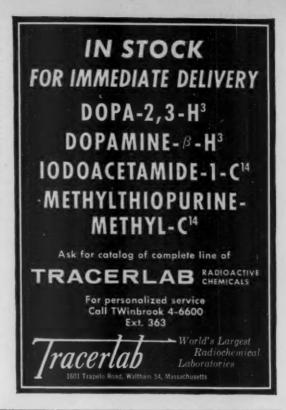
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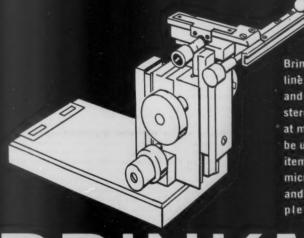


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Instrument carrier (Fig. 1) that is used in making oceanographic measurements is said to remain at the desired depth regardless of changing speed of the tow ship. Complete stability is said to be achieved at speeds up to 20 mi/hr. Data gathering instruments are carried in a compartment measuring 12 by 21/2 by 11/8 in. The compartment can be sealed watertight, or the electronic instruments and circuitry can be potted. Data gathered by the instruments are transmitted to the towing ship through a 3/32-in, coaxial towing cable. When used for underwater acoustic measurements, the carrier can have a hydrophone mounted in its nose and an impedance matching transistorized preamplifier in the instrument compartment. Hydrophone sensitivity is -88 db. (Braincon Corp., P.O. Box 312, Marion, Mass.)

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**Wave-form translator** operates with an x-y recorder to produce a permanent record of repetitive functions displayed on an oscilloscope at high speed. Operation is based on recurrent simultaneous sampling of both vertical and horizontal oscilloscope deflection plate voltages at intervals equal to, or almost equal to, the wave-form period. The sample signals are fed to the translator's high-impedance input, and each signal is then applied to an individual sampling clamp. An amplitude comparator equates the signal to a slowly varying reference voltage derived from a ramp generator, and the resulting strobe pulse is used to drive the clamps. As the strobe traverses the trace, the outputs of the x and y clamps are measurements of the instantaneous coordinates of the scanning strobe point. These d-c signals are applied to the axes of the x-y recorder to produce a permanent record of the wave form. For identification purposes, the strobe pulse is also transmitted to the intensity (or z) axis of the oscilloscope to form a bright spot on the trace at the point being sampled.

The translator also provides a manual sampling mode. Strobe position is selected by varying a single-turn potentiometer that controls the reference voltage applied to the amplitude comparators. If desired, the translator can be operated directly from the test device without an intermediate oscilloscope. In this case, the electrical signal characteristics must be of the same form and amplitude as those supplied by an oscilloscope, and an external trigger signal is required. (F. L. Moseley Co., 409 N. Fair Oaks Ave., Pasadena, Calif.)

Circle 3 on Readers' Service card

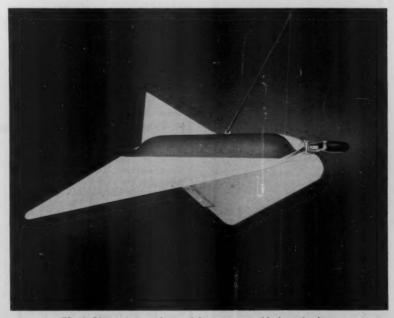


Fig. 1. Instrument carrier used for oceanographic investigation.

The information reported here is obtained from manufacturers and from other sources considered to be reliable. Neither Science nor the writer assumes responsibility for the accuracy of the information. A Readers' Service card for use in mailing inquires concerning the items listed is included on pages 1465 and 1563. Circle the number of the items in which you are intersected on this cord.

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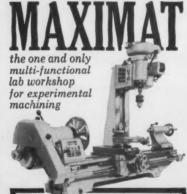
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A shutter segment interrupts the light beam once each revolution to allow the sample to be changed. The underside of this shutter segment is a reference reflectance surface spectrally similar to the products being sorted. While this surface is in the viewing area, a second set of filters rotates through the beam to provide reference signals for system calibration. The phototube supply voltage is adjusted automatically to provide a constant output for the green reference signal. The amber reference signal provides information for manual adjustment of the lamp's color temperature.

The analog-signal amplitudes are assigned to discrete categories necessary for the sorting process by a voltage digitizer. The measurements are stored in binary form until the measurements for a single sample are completed. The stored information is examined electronically to assign a color category to the sample, and a selection matrix assigns various exits to selected color categories. As many as 30 color determinations per second can be made, but the degree of color resolution obtained is inversely proportional to the rate of operation. (Allied Research Associates, Inc., 43 Leon St., Boston 15, Mass.)

Circle 4 on Readers' Service card

Electron beam systems, the series LB-100, cover a range of powers from 3 kw at 10 kv to 9 kw at 30 kv. The systems include electron guns, power supplies, and controls. Magnetic deflection of the beam is provided over a 3-in.-square area. Beam energy may be pulsed, regulated over a wide range, and varied in focus. The systems may be adapted for programmed automatic operation by using the deflection capability to produce desired welding or etch patterns on a work piece. A wide range of standard pumping systems,

manipulating devices, and monitoring systems can be provided as optional equipment. (GVC Electron Heating Corp., 81 Hicks Ave., Medford, Mass.)

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Physiological stimulator, for research and clinical work in human vision, generates a high-intensity burst of light controlled in several modes. The light source is a glow tube with an essentially white spectrum. In continuous-wave (CW) mode, the light flickers continuously at flicker frequency adjustable between 0.1 and 60 cy/sec. In gated-CW mode, an external pulse turns the flicker generator on and off. In gated-pulse mode, the source is turned on by an external signal and does not flicker. Source diameter is 1/16 in. (Industrial Control Co., Central Ave. at Pinelawn, Farmingdale, N.Y.)

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Digital integrator, recorder, and controller accepts the output signals from a variety of analytical instrumentation detectors and converts them to digital records of both time of occurrence and relative area of signal peaks. Output may be in digital-printer or typewriter format, punched cards or tape, or magnetic tape. Integration is performed digitally. The control unit of the instrument senses the start and end of data output signal peaks and also the instant of maximum signal. Logic circuits program the application of integral and peak-time values to the recording equipment. The system operates with an input of 100 mv full scale. Input impedance may be specified in

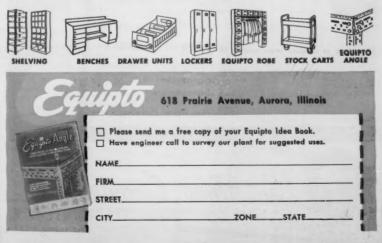


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the 10- to 100-kohm range. Integrator capacity is six digits, but additional capacity is available. Accuracy is said to be ±0.1 percent of full scale. Sensitivity to rate of change of detector voltage is said to be better than 0.1 mv/sec, adjustable to allow maximum precision compatible with freedom from nuisance readouts. Signal peaks spaced as closely as 2 sec apart can be processed. (Infotronics Corp., 1401 S. Post Oak Rd., Houston 27, Tex.)

Circle 8 on Readers' Service card

Cathode-ray display system will simultaneously display on a 7-in. tube up to eight input signals superimposed on an electronically generated coordinate

system. The signal wave forms and the coordinate system are displayed simultaneously to eliminate errors from distortion and nonlinearity. Accuracy of plotting is said to be ±0.2 percent. Fullscale deflection is provided by ±100 volts. An optional preamplifier permits expansion and zero-shifting of small signals. A choice of display periods ranges from 25 msec to 50 sec. Input signals and voltages for producing coordinate lines are sampled every 62.5 usec for display. The time reference is provided by a crystal oscillator that triggers a vertical flying scan deflection system. (Philbrick Researches, Inc., 127 Clarendon St., Boston 16, Mass.)

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Neutron detector is a solid-state device with low gamma sensitivity and millimicrosecond response. The detector is available in two sizes, 5 by 5 or 10 by 10 mm, and with uranium, boron, lithium, or hydrogenous material coatings. A three-pin connection arrangement sockets into standard transistor bases. Operation is at 25 volts. (Solid State Radiations, Inc., 9926 W. Jefferson Blvd., Culver City, Calif.)

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Photographic exposure repeater, designed for production of precise photomasks required by the transistor industry, is built around a two-coordinate comparator. The equipment permits positioning of patterns with accuracy of ±0.0004 in., precise focusing, and precise setting of reduction ratio. The apparatus has a programming mechanism capable of performing various combinations of step-and-repeat operations for automatic exposures; operation can also be manual. (Geophysics Corporation of America, Bedford, Mass.)

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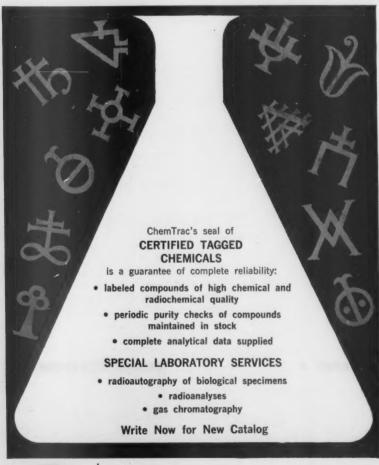
Bi-directional counter is designed for machine position readout. An incremental pulse transducer provides a wide range of resolutions with self-contained bi-directional logic. Capacity of the instrument is 5 or 6 digits with numerical readout tubes at count rates up to 5000 counts per second. Selector switches permit setting numbers into the counter. (Veeder-Root Inc., Danvers, Mass.)

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Accelerometers, the series PAL-1S and PAL-1P, are self-contained instruments said to provide accuracy of 0.1 percent. They operate on the forcebalance servo principle in which the d-c current required to restrain a pendulous seismic mass measures the acceleration. Natural frequencies to 600 cy/sec or higher are available in ranges as low as ±2 grav. Total power requirement is ½ watt. (Palomar Scientific Corp., Palo Alto, Calif.)

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Galvanometer servo system combines a D'Arsonval movement with a precise film-type potentiometer. A signal fed into the meter is compared to a voltage obtained from the feedback potentiometer. If the meter movement position does not correspond to the position called for by the magnitude and polarity of the input signal, an error signal results which, after amplification by a self-





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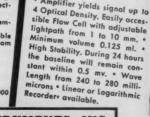
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contained transistorized amplifier, drives the meter movement to correct the error. Response time of 50 msec full scale is said to be achieved by virtue of the high ratio of torque to inertia. Power required for position indication is 1 watt; maximum accelerating power is 1.5 watts.

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is set by a direct-reading dial; overpressures up to 250 lb/in.<sup>2</sup> are tolerated. Actuation of the units is said to be completely independent of absolute working pressure. (Pall Corp., Glen Cove, N.Y.)

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Count-rate meter is a transistorized instrument for use with Geiger-Mueller tubes, proportional detectors, or scintillation detectors. Five count-rate ranges up to 10° counts per minute are provided with probable-error settings of 2, 5, 10, and 15 percent for each range. Input sensitivity is said to be better than 1 mv. The instrument is capable of driving both 0- to 1-ma and 0- to 100-mv recorders. A 3000-volt power supply is included. (Nuclear Corporation of America, Denville, N.J.)

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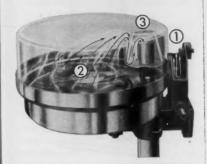
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Resistance network analog is designed to solve problems involving Poisson's. Laplace's, and special cases of Maxwell's equations. Over-all network accuracy is said to be better than one part in 10,000. The analog is a selfcontained system including the resistance network board, 150 current injection potentiometers, three regulated d-c power supplies, a digital voltmeter. and a vacuum-tube voltmeter. It may be combined with a digital computer for accurate calculation of electron trajectories. Programs for the IBM 704, and 7090, and Philco 2000 digital computers are available. (Litton Industries, 960 Industrial Rd., San Carlos, Calif.)

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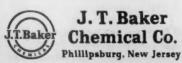
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ranges and ±0.5 percent for one decade. A three-decade unit covering the range from 20 cy/sec to 20 kcy/sec provides an accuracy of ±2 percent. A plug-in oscillator permits alignment of span and zero. (Houston Instrument Corp., P.O. Box 22234, Houston 27, Tex.)

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Thermocouple reference junction is a temperature control device that provides a constant thermocouple reference temperature of 250°F with a 24-channel capacity. Uniformity between junctions is 1°F, and ripple is less than ±1°F. Regulation through the ambient range -65° to +165°F is said to be less than 3°F. The device measures 3¼ by 3¼ by 5¼ in. and weighs less than 4 lb. Nominal power consumption is less than 5 watts. (Astra Technical Instruments Corp., 12930 Panama St., Los Angeles 66, Calif.)

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Fetal-heart monitor provides constant visual and audible monitoring of the fetal heartbeat during labor and through delivery. Any irregularity, or a drop below the danger level of 100 beats per minute, is instantly recorded. Monitoring is performed by means of electrodes attached to both the mother's body and to the fetus, still contained within the womb. The heartbeat is displayed on an oscilloscope screen; a meter indicates heart rate. A permanent trace may be recorded by attaching a standard electrocardiograph. (Hemathermatrol Corp., 5334 Rockville Rd., Indianapolis, Ind.)

Circle 24 on Readers' Service card

Depth recorder surveys depth in three ranges—400 ft, 400 fathoms, and 4000 fathoms—at repetition rates of 360, 60, or 6 per minute, respectively. Resolution on the 400-fathom range is said to be better than 1 fathom. The fully transistorized instrument has a display width of 19 in. Recording is made with a resilient helix and stainless-steel endless loop electrode and electrosensitive paper. (Alden Electronic & Impulse Recording Equipment Co., Westboro, Mass.)

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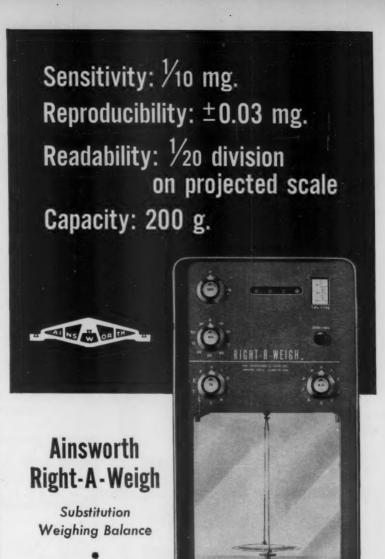
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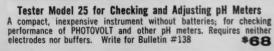
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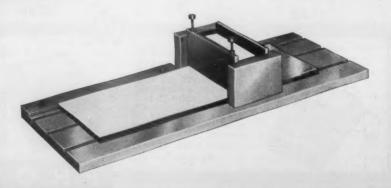
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# Letters

## U.S. Strategy

There appeared recently in "Science and the news" two articles entitled, respectively, "Grand strategy: The views of the Administration and the War College do not seem to coincide" [Science 134, 543 (25 Aug. 1961)] and "Grand strategy: The Administration has a problem that it would rather not deal with in public" [ibid. 134, 602 (1 Sept. 1961)]. Both articles are signed H.M. The references in both articles to the Foreign Policy Research Institute of the University of Pennsylvania contain a number of errors which require correction.

1) You are free to ascertain, by direct inquiry to the Department of Defense, the relationship of this institute with the National War College. In any case, this relationship has not been as stated in the article. Furthermore, may I call attention to the fact that it is not the mission of the National War College to train "promising young officers." The great majority of the students of the National War College hold the rank of colonel or of Navy captain. Their median age is a matter of record.

2) Both articles contain comments purporting to show that a publication of the Foreign Policy Research Institute entitled A Forward Strategy for America (Harper, New York, 1961) contains proposals for preventive war. In support of this allegation the author of the article quotes from chapter 2 of the book. Specifically, he quotes a part of a passage (p. 15) that reads as follows.

In the Cold War, the Soviet Union has one overriding advantage, namely, its freedom to opt for a sudden surprise attack. The United States, on its part, has deliberately rejected this option for moral reasons and has done so despite the enormous military disadvantages which the rejection entails. American strategy—a strategy dictated by moral considerations—facilitates a Soviet strategy of all-out war. But it does not ease necessarily the over-all strategic problem of the Soviets. If the Soviet Union were to rely on a strategy of piecemeal conquest, the very success of Soviet "nibbling" could push the United States

into a nuclear conflict at some point where its vital interests left no other choice. Unless the United States could be induced to surrender or be subverted by an internal revolution, both of which contingencies are most unlikely, a reversal of American strategy toward pre-emption may, sooner or later, be in order. Precisely because of the devastating power of nuclear weapons and because the United States continues to be the only other major nuclear power besides the Soviet Union, a reversal of U.S. strategy remains possible almost to the last minute. Even at a moment when the United States faces defeat because, for example, Europe, Asia and Africa have fallen to communist domination, a sudden nuclear attack against the Soviet Union could at least avenge the disaster and deprive the opponent of the ultimate triumph. While such a reversal at the last moment almost certainly would result in severe American casualties, it might still nullify all previous Soviet conquests.

The italics are those of the text. This passage is quoted here in full. It is perfectly clear that this passage does not contain any policy proposal. It gives our understanding of the impact of nuclear weapons upon international politics. Anyone is welcome to debate the logic of our understanding; no one can find in it a recommendation for American strategy.

In chapter 5 of the same book the authors do advance proposals for an appropriate United States strategic posture. They preface their proposals with the following words (p. 119).

A policy of preventive war, however, is anathema to our sense of values. Moreover, a preventive war must be launched by surprise; preparations for it must be made in secret. The open societies of the West practically rule out such a policy choice.

The authors' enumeration of the requirements of an appropriate U.S. military posture begins with the following statement (p. 124).

First, we need a basic deterrent posture, i.e., invulnerable offensive forces for second-strike attack on the U.S.S.R. Invulnerability implies that we decide what kind of residual capability we need to implement our strategy and then make certain that at least this percentage of our retaliatory force will be safe even after we have absorbed the first blow.

This, as far as can be determined from public statements of the Kennedy Administration, is the current U.S. policy toward nuclear war. There is a question of judgment as to the degree of preparations which the U.S. must make to fulfill its military commitments. particularly to have an invulnerable second-strike force. It is essential in dealing with American strategy to consider the role of nuclear weapons. We do not consider their use inevitable. In fact, the book states (page 6): "the reality of our age is, however, that the most important battles may not be fought by exchanges of nuclear firepower, but, like the conflicts of the sixteenth and seventeenth centuries, will consist of maneuvers and diversions designed to achieve a decisive advantage by one side or the other" (the italics are those of the book). The central concern of the book is how the United States can best coordinate all its efforts diplomatic, economic, psychological and cultural-toward the creation of a world environment in which freedom might flourish. In order to attain this end, the United States must search for policies and create capabilities that will permit it to choose an alternative other than total surrender or total war-a dismal choice which the Communist rulers seek to force upon us. Again, as far as one can determine from policy statements, President Kennedy is pursuing a policy which is generally consistent with that proposed by the authors of A Forward Strategy for America.

The writings published by the Foreign Policy Research Institute do not contain any proposals for preventive war. No member of this institute has, in writing or by word of mouth, advocated that the United States embrace a strategy of the first strike.

- 3) The second article by H.M. refers to a report by a secondary source according to which a government contract granted to an unidentified research institute has been sharply cut. No government contract that has been entered by this university on behalf of this institute has been cut.
- 4) The same article states that "even the eight associate authors of the book [A Forward Strategy for America], who contributed to one chapter or another, do not necessarily subscribe to the over-all view of the book." A Forward Strategy for America was published 8 months ago. During this period none of the "eight associate authors of the book" have expressed any disagreement

with the "over-all view of the book." The book was prepared in close consultation with the individuals listed as contributors to the book. During the course of these consultations they were free to voice their dissent with the "over-all view." Not a single one did; not a single one has done so since.

5) The same article contains the following statement: "This report, perhaps unavoidably, has given the entire movement associated in one way or another with the Forward Strategy a more monolithic character than it actually has."

I know of no movement—"monolithic" or otherwise—associated with the "Forward Strategy." I herewith state categorically that the 'Foreign Policy Research Institute is not associated with any "movement." A political movement—and the author of the article can have no other movement in mind—must be organized in order to justify the term. This institute has no connection with any political movement aimed at promoting any particular set of political doctrines or strategic concepts. Members of this institute, like most Americans, are members of one of our two

great political parties and of a variety of civic, professional, and scientific organizations. The Foreign Policy Research Institute has no affinities except those that are explicit in its status as a research group within the University of Pennsylvania.

6) The author of the two articles seeks to establish a covert relationship between A Forward Strategy for America and another book published previously by the Foreign Policy Research Institute-namely, American Strategy for the Nuclear Age. According to H.M., the purpose of the latter book was to soften and prepare the way for A Forward Strategy for America, which, according to him, maintains that the U.S. must prepare for launching a surprise attack against the Soviet Union. Although this assertion is made repeatedly, H.M. is careful to protect himself by an ingenious literary device against the charge of having disregarded the actual text of both books. He concedes that the book does not contain a proposal for a policy of striking "a surprise knock-out blow" at the Soviets. Yet he has mastered this problem by writing as follows:

This policy is not specifically stated in the book; it is merely the only realistic policy that follows from the premises of the book, and the members of the Foreign Policy Research Institute consider themselves, above all else, as realists.

His conclusion thus boils down to an attempt to read our minds rather than our writings. This procedure can be characterized in various ways; it cannot be mistaken for scientific method.

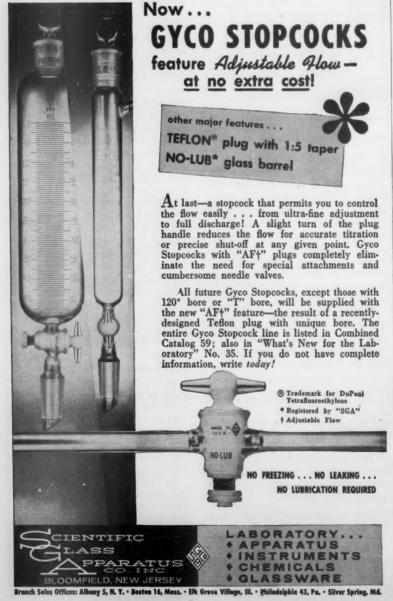
ROBERT STRAUSZ-HUPE

Foreign Policy Research Institute, University of Pennsylvania, Philadelphia

I could argue with a number of the points in Strausz-Hupé's letter, but overall there is no doubt that the articles contain substantial flaws. I think the letter of censure is well deserved.—H.M.

## Drugs and the Kefauver Bill

The following statement appeared recently in "Science and the news" [Science 134, 89 (14 July 1961)]: "Kefauver has produced evidence that a sizable proportion of the new drugs patented and put on the market are not in any significant way new. They involve merely minor changes in the molecular structure of an already avail-



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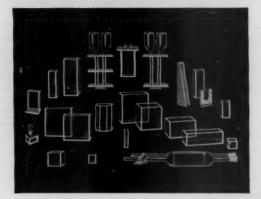
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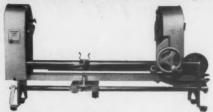
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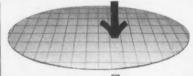
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Cooke, G.M., et al., 1957, STAIN TECHNOLOGY, 32:2, pp. 63-66, Mar.

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able, and perhaps unpatented, drug: their only advantage is that they can be patented, promoted as a new drug, and thus be relieved of direct competition with similar drugs identical in their medical effects. The Kefauver bill would require that a drug be significantly different in its effects as well as in the details of its molecular structure in order to be patentable."

I wish to call attention to the fact that Senator Kefauver's generalization does not apply to most psychoactive drugs, for the brain is more sensitive than any other organ to the chemical structure of a drug. Let me say in the first place that in most instances the first member of useful groups of drugs was found by accident, as a trained worker took advantage of a chance observation. Further development, however, came from the application of the principle of molecule manipulation. This applies to meprobamate (trade names, Miltown and Equanil), one of the drugs most widely used in the management of the neuroses, and chlorpromazine (Thorazine), a member of the phenothiazine group of drugs, which is employed more than any other in the treatment of the psychoses.

Mephenesin was synthesized to provide a drug affording muscular relaxation. In the course of clinical study it was noted that the muscular relaxation was sometimes accompanied by tranquilization. This finding led to the synthesis of meprobamate, which has stronger central effects than its parent substance, and today this drug is widely used as a mild tranquilizer, especially for the treatment of the neuroses, as it relieves anxiety and tension. Further development of meprobamate-namely. the formation of mebutamate-yielded a drug with less marked tranquilizing action but with intensified power to lower blood pressure. Additional molecule manipulation vielded carisoprodel. which evokes more pronounced muscular relaxation than mephobamate.

Largactil, known as chlorpromazine in the United States, was administered to disturbed psychotic patients in France because of its sedative action. This new drug, however, showed a capacity to reduce psychotic excitement not found in earlier drugs, and it has achieved wide usefulness as a strong tranquilizer: The sedatives previously employed could not relieve hyperactivity and calm the patient, nor could they reduce the intensity of hallucinations and delusions without inducing sleep. The other

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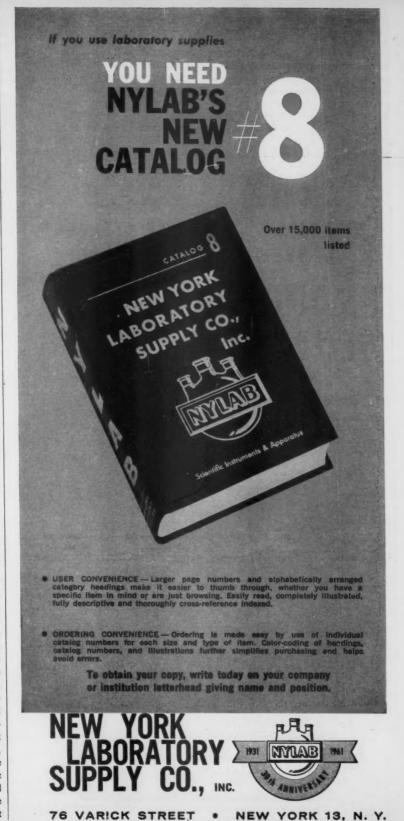
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phenothiazine drugs now used were developed by molecular manipulation, and they perform the same actions but to different degrees. The stronger ones require a smaller dosage and evoke lower degrees of sedation and fall in blood pressure. Convulsions and rashes are less frequent, while jaundice and a decrease in white blood cells occur more rarely than with the weaker phenothiazine derivatives. But for the advantages of the more potent members of the phenothiazine group, and their greater stimulating powers, we must pay the price of an increase in undesirable neurological effects such as tremor, motor restlessness, spastic muscular conractions, and involuntary muscular movements. The wide variations among the various phenothiazine drugs permit the discerning psychiatrist to select the one most suitable for an individual patient, through his knowledge of the greater tranquilizing action of the weaker phenothiazines, the greater stimulating effect of the stronger phenothiazines, and the characteristic intensities of the side reactions, which differ with each member of the phenothiazine group.

Altering the molecular structure of some parts of the phenothiazine molecule yields drugs which produce behavioral effects not evoked by phenothiazines. The substitution of a diethylene linkage (-CH<sub>2</sub>-CH<sub>2</sub>-) for the sulfur atom (S) produces imipramine (Tofranil), and instead of a tranquilizer we have an antidepressant drug.

These facts, and many more like hem, reveal the importance of molecule manipulation in research but do not answer specifically Senator Kefauver's objection to patenting drugs which seem to have similar actions despite molecule manipulation. The diversity of reactions to the same drug by different patients is well known. It is true that most patients react in similar ways to a given phenothiazine, but it is a remarkable fact that psychotic patients who are not improved by one of two apparently equivalent phenothiazines may receive benefit from the other. Clinical use of new phenothiazine reveals that some patients who were not elped by the previously known phenohiazines respond to the new one. It would seem that, with enough patience, phenothiazine derivative could be found to improve every schizophrenic to some degree. Such a prospect could not be realized if drugs that produce similar effects in most patients were not



developed and administered to patients whose reactions differ from those of the majority. If the restrictions suggested by Senator Kefauver were adopted, they would hinder the development of many useful drugs. This would change our present situation, so full of promise, to one of restricted output, not conducive to future progress.

HAROLD E. HIMWICH

Research Division, Galesburg State Research Hospital, Galesburg, Illinois Being a research chemist in a drug firm I am perhaps biased, but I feel that a protest should be registered against Howard Margolis's account of the hearings on the Kefauver omnibus bill for regulation of the pharmaceutical industry. Margolis does not report on Senator Kefauver; he propagandizes for him.

The tenor of the article is indicated by the last two sentences: "For all these reasons a far more intense controversy surrounds the bill than a casual reading of Kefauver's bill would suggest. For the bill, on a casual reading, appears to contain nothing more than a series of minor technical changes in laws of whose existence the public is scarcely even aware." Now the changes proposed by the bill are not minor, and what is so troubling about the account in Science and the attitude of Kefauver is the complete failure to understand that these changes are a grave threat to the future of research in medicinal chemistry. One may just as well expect the modern theater to flourish without copyright protection.

The pharmaceutical industry has been accused of excessive price-charging by Kefauver. The industry has replied that prices are generally not excessive, and that one factor which the senator has failed to take into account with regard to new drugs is the high cost of research. Kefauver answers in his omnibus bill with licensing regulations which will effectively eliminate research. Drug prices will drop if research is stopped, but there is a catch—there will be no new drugs.

Senator Kefauver will not pay for progress. He has the viewpoint of Ortega y Gasset's "hyperdemocrat," who "wants his motor-car, and enjoys it, but believes that it is the spontaneous fruit of an Edenic tree. In the depths of his soul he is unaware of the artificial, almost incredible, character of civilization, and does not extend his enthusiasm for the instruments to the principles which make them possible" (Revolt of the Masses, chap. 9).

Margolis repeats, with apparent approval Kefauver's contemptible suggestion that the American Medical Association has come to the defense of the drug industry solely to protect the advertising revenues of its journals.

One expects a better understanding of science in *Science*.

EDWARD F. ROGERS

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61 Kings Highway, Middletown, New Jersey

The point of the article was exactly the one made in Rogers' letter: namely, that, as the two sentences he has quoted suggest, the bill is designed to have a profound effect on the drug industry even though a casual reading might suggest merely a series of minor technical changes. The article did not say, and so far as I can see did not suggest, that the sole reason the AMA supported the industry was to protect its advertising revenues.—H.M.

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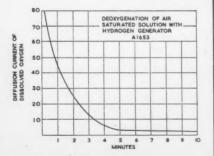
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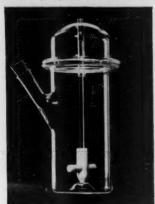
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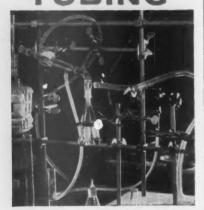
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## Rainfall Singularities

This letter has been prompted by the appearance of a recent lead article in Science [134, 361 (11 Aug. 1961)]. Survey articles of this type, touching as they do on research problems which fire the public imagination, serve a useful purpose in presenting a comprehensive picture of the state of the art. It is unfortunate that Fletcher was not aware of the difficulties in the analysis of the rainfall data which he discussed, and their implications. There is now a good deal of evidence to suggest that there are no world-wide rainfall singularities. In the conclusion to his article Fletcher states, "If, however, as appears to be the case, the rainfall singularities are real, then the meteor hypothesis is the only one which has been advanced as yet which seems capable of explaining them." Logically, if the rainfall singularities are not real, then no hypothesis or speculation is necessary. Let us look at the observational evidence for the existence of rainfall or other geophysical singularities.

As Fletcher has noted, it is difficult to estimate statistically significant departures when a number of records have been arbitrarily lumped together. This is particularly true when there has been no effort to select observations that are independent of one another in time or space. Bowen's original work combined data from 300 stations for about 50 years ("15,000 station years"). The geographical distribution of stations is shown in Table 1.

As is well known to meteorologists, the spatial correlation of rainfall over small regions (for example, Great Britain) is quite high. Not only does this spatial correlation decrease the number of the degrees of freedom of the resulting curve (see Fletcher's Fig. 6), but it introduces a bias into the estimation of what constitutes "world-wide" rainfall. Therefore the "15,000 station years" are equivalent to only a small fraction of this number of independent observations. This criticism is as valid now as it was when Bowen's work was first published.

However, Bowen's evidence seemed to be supported by the later work of Brier. Comparing two rainfall time series, independent of each other and of Bowen's original data, Brier stated that "these results [Brier's] lead to the conclusion that there has been a strong tendency for precipitation anomalies (both high and low) to occur on specific calendar days." Recently, R. Sha-

Table 1. Geographical distribution of stations.

Area	Stations (number)	
Argentina		
Australia	50	
Great Britain	100	
Japan	32	
Netherlands	5	
New Zealand	58	
Union of South Africa	10	
United States	48	

piro and N. J. Macdonald [J. Meteorol., in press], using Brier's data, showed that the relationships between the rainfall series were due solely to a coincidence of days of average rainfall. This led to the conclusion that "Brier's results may be said to show a weak tendency for the association of nonanomalies of precipitation on specific calendar dates." Therefore, Brier's work cannot be considered evidence in support of the existence of rainfall singularities.

Fletcher indicates that Dmitriev and Chili also found rainfall peaks that corresponded to those in the Bowen data. Unfortunately, no reference is given.

Again, according to Fletcher, "Bowen found a correlation between his rainfall peaks and intense meteor showers occurring about 30 days previously, as shown in [Fletcher's] Table 1." Because of the number of showers, their duration, and the 28 to 32 days that Bowen actually allows for verification, the results shown could easily be obtained by chance, as a simple chi-square test will show.

As further support, Fletcher goes on to cite the cirrus-cloud study by E. K. Bigg [J. Meteorol. 14, 524 (1957)]. Bigg claimed some association between the mean percentage of sky covered by cirrus and Bowen's 300-station rainfall curve. A simple calculation shows that the linear correlation coefficient between the two curves in Bigg's paper is only + 0.24. Even if the observations were completely independent of one another (which they are not), the correlation does not even approach the 5-percent significance level. It is not surprising, then, as Fletcher has also noted, that Braham failed to find any confirmation of Bigg's results.

It is quite apparent that the evidence for the existence of rainfall singularities will not stand careful scrutiny. It seems irrelevant, then, to speculate on physical explanations.

NORMAN MACDONALD FRED WARD

Geophysics Research Directorate, Air Force Cambridge Research Laboratories, Bedford, Massachusetts ions. iber) 10 58

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The comments of Macdonald and Ward emphasize the fact that controversy still rages over almost all aspects of the meteor hypothesis. It is perhaps unfortunate that decisive physical tests of the theory are lacking and that most arguments concern the statistical significance of apparent correlations between various time series. It is a notorious fact that statistics can be made to support almost any proposition in a sufficiently complicated situation, and both the proponents and the opponents of the theory have often erred in drawing unwarrantedly strong conclusions from inadequate sets of data.

The criticism of the data upon which Bowen's world rainfall curve was based appears to have a certain validity. Ideally, some sort of weighting should be introduced to take account of the clustering of sets of stations, but any such doctoring of the raw data brings with it further possibilities of bias. It would, however, be most instructive to see the results of some such independent and impartial treatment of the same data.

It is impossible to comment on the criticism of Brier's conclusions until the paper referred to has been published. The reference to the Russian work was omitted as not being readily available to readers. It is as follows: A. A. Dmitriev and A. V. Chili, Trudy Inst. Morskogo Gidrofizicheskogo 12. 181 (1955?).

As my original article was intended to imply, I do not believe that the existence of world-wide rainfall singularities has been either unequivocably demonstrated or finally discounted. The same must be said of the meteor hypothesis itself.

N. H. FLETCHER

Department of Physics, University of New England, Armidale, Australia

#### Complete Disarmament

The editorial "Arms control and selfcontrol" [Science 134, 249 (28 July 1961)] speaks of "present efforts to show how the Soviets put up obstacles to disarmament." The value of these efforts appears to be questionable as long as we continue to dismiss the Soviet 4-year plan for complete and universal disarmament as unrealistic or as propaganda. Our present attitude toward this Soviet proposal would suggest that it is we who do not wish to disarm, espe-

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cially in view of evidence that the U.S.S.R. intends this proposal seriously and considers complete disarmament to be a realistic policy.

Some of this evidence might be summarized as follows: (i) Public speeches by Soviet leaders indicate that they, like some of our own leaders, are worried about the consequences of a continued arms race—notably the increasing probability of war. The U.S.S.R. experienced widespread devastation and the death of some 25 million people as a result of the German attack in World War II.

**PATHOLOGY** 

Present Soviet leaders apparently wish to avoid a repetition of this experience; the new 20-year program of the Soviet Communist Party is reported to give top priority to "saving mankind from devastating world war." (ii) Under the Soviet system of nationalized industry, continued expenditures on armaments represent a wasteful drain on the national economy, with no particular profit to anyone. (iii) The detailed disarmament plan submitted by the U.S.S.R. to the United Nations in 1960 provides for international control and inspection of

MICROBIOLOGY

all stages of disarmament as well as an international police force and does not include any veto on control measures. Premier Khrushchev has recently repeated his statement that the U.S.S.R. is prepared to accept any control measures proposed by the Western nations if we in turn agree to the Soviet proposal for general and complete disarmament.

Regardless of our opinions about the U.S.S.R., most of us would agree with the Soviet leaders that a world free from wars and the fear of wars would be desirable. If we do not wish to be condemned by "uncommitted persons and nations," we cannot now afford to dismiss the Soviet disarmament proposal without more serious consideration than that of its propaganda value.

The question of complete disarmament involves the decision whether the products of scientific research are to be used for the destruction or for the enrichment of human life. If this choice is open to us now, scientists themselves bear both individual and collective responsibility for the decision.

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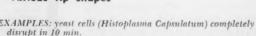
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# **Exporting Universities**

Although I do not totally disagree with the ideas of Arthur F. Burns and H. V. Fairbanks [see *Science* 133, 1557 (1961); 134, 225 (1961)], I wish to make the following observations as a foreign student under the Fulbright program.

Very often the foreign student finds it difficult to locate an educational institution offering a suitable program of training bearing on the needs of his country. Perhaps for financial reasons he is forced to enter a school which offers him support, no matter what the nature of the training is going to be. This does not depend on whether or not he makes the choice of the institution before he arrives in this country; when he arrives in this country he has a high hope of making his training most profitable to his country. The choice of a wrong institution results in waste of the talent and resourcefulness of the individual concerned. It is probably for this reason that a foreign student gets discouraged and dissatisfied when he returns home, and not because he is unable to "teach what he has learned."

Further, it is not entirely true that a lack of identical scientific and educa-

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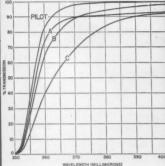


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tional facilities in the home country would prevent a student trained abroad from teaching what he has learned. I feel that it is the principles one learns that are most important, rather than what tools he uses to learn them. As long as the student is able to adapt these principles to conditions at home. he will feel no dissatisfaction when he returns home. Besides, what the student learns outside the classroom and the laboratory goes a long way toward educating the individual and ultimately, through him, many others. In this sense, I feel, students should always be encouraged to visit foreign countries to further their own education and ultimately be useful to their countries.

The idea of "exporting universities," however, is a good one, but it would create more problems than we imagine. S. K. KRISHNASWAMI

University of the Pacific, Pacific Marine Station, Dillon Beach, California

# **Discovery and Obligation**

The editorial "The jinni in the bottle" [Science 134, 359 (11 Aug. 1961)] ends with the curious questions whether the scientist can be expected "to differentiate his role as a scientist from his role as a citizen," and what can fairly be asked of a scientist in relation to anticipated social consequences of his discoveries. It is implied in these questions that his scientific activity divorces the investigator from his responsibilities as an ordinary human being. No such assumption is ever made, nor is its necessity felt, if the economic and social consequences of discoveries are pleasant ones, conferring benefit on humanity. It is even taken for granted, and justly so, that a scientist shall, if necessary, battle the vested interests, academic or otherwise, and openly oppose entrenched ideas and practices. once his discoveries have convinced him that doing so is required by the public welfare. Many of our greatest scientists have assumed this responsibility at a heavy cost in personal comfort and peace. Why should the situation be different if the potential consequences of a discovery bode ill for humanity?

Your editorialist concludes reasonably that there is little point in recoiling from a discovery and in putting "the jinni back into the bottle," since, "if he stops, someone else will continue." Un-

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WALTER LANDAUER Department of Animal Genetics,

University of Connecticut, Storrs

With reference to the editorial "The jinni in the bottle," we should never allow any jinni (new knowledge) to be kept in the bottle.

Neither war nor peace is an act of God; both are caused by man, and it is important to realize that knowledge used to fabricate weapons to wage war may ultimately be useful for the waging of peace. The nitrogen mustards and organic phosphates, gases for war, ultimately proved to be of value in cancer chemotherapy and insect control, respectively. Atomic energy itself has also led to weapons for peace heretofore visualized only by the prophets of science.

What man has made for war man can also use for peace.

R. H. ADAMSON

Bethesda, Maryland

The writer of the excellent editorial "The jinni in the bottle" begins with the interesting pastime of undoing history in order to rewrite it, but proceeds to the very real question of whether a scientist can separate his role of scientist from his role as citizen.

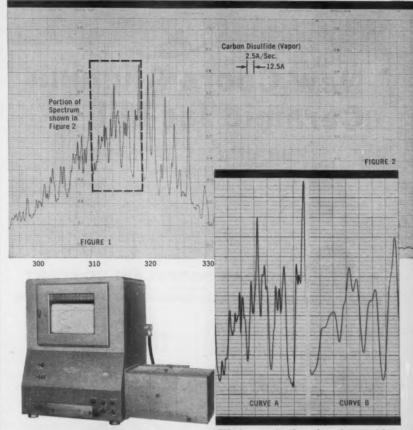
The question is raised in connection with the development of nuclear weapons, resulting from basic scientific work in nuclear physics, and extends to the possibility of undesirable effects if large-scale control of weather, genetic material, and so on should become possible.

The dichotomy, it seems to me, is not between the scientist as scientist and as citizen but between the scientist as scientist and as human being. If a scientist anticipates abuse of his discoveries as a probable future event, he should discontinue his work; otherwise, he personally becomes morally and socially responsible for this abuse. The mere fact that, if he discontinues, somebody else may pick up the threads and continue does not absolve him from his



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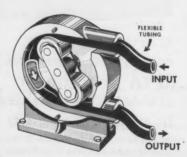
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responsibility. If this reasoning were to hold, it would absolve any driver arrested for a traffic violation because he could say if he had not speeded. somebody else would have.

In former times, this sense of personal responsibility was strongly developed, and it may be well to remember that Leonardo refused to disclose the invention of a submarine because he foresaw the evil use to which such an invention might be put.

VICTOR PASCHKIS

Columbia University, New York

# Classroom Teaching and Research

Your editorial "The system," in a recent issue of Science [134, 159 (21 July 1961)] deals with what I regard as one of the most important and troublesome problems facing our universities, but one which is generally ignored. Partly as a result of our desire to increase research activity and partly because of the availability of research funds in nearly all fields, the best minds in our universities are being diverted from undergraduate teaching to research and graduate teaching.

Our energetic young staff members try to get out of beginning courses as soon as possible in order to have more time for research. If the present trend continues, only those staff members lacking the initiative and imagination to obtain research grants will be left to do our undergraduate teaching. We can scarcely expect such people to be effective in attracting bright young students into graduate school. In fact, they cannot even give the general student body the kind of background it needs.

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The effects on undergraduate teaching of our excessive preoccupation with research on university campuses is seen in the fact that most of our graduate students come from colleges where little research is done, and relatively few come from universities where research occupies much of the time and energy of the staff.

You suggest that perhaps undergraduate teaching will be left largely to the four-year colleges, but they also are beginning to develop research programs which will divert an increasing proportion of the time and energy of their staff members away from teaching. As I hear college administrators asking for money to develop research programs, I wonder if they realize how this may affect their teaching programs.

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Good undergraduate teaching and good research are not incompatible, but they are competitive, and whichever promises the most rewards is likely to take precedence. Young college staff members distrust the claims of administrators that they will reward good teaching, because they have seen too much evidence that research and publication are rewarded even better. It takes many years for an individual or a department to build a reputation for good teaching, but a few good papers will establish a reputation for research rather quickly.

I doubt if many of our university administrators have given serious attention to this problem. Most of them have encouraged staff members to take as much research money as they can obtain and have shut their eyes to the consequences. Perhaps administrators need to reconsider their objectives and the value scales used for determining pay and promotion. It seems possible that a well-taught freshman course and a few good students inspired to go into graduate school may be a greater accomplishment for most of us than our research.

PAUL J. KRAMER National Science Foundation, Washington 25, D.C.

Your editorial entitled "The system" is the sort of challenge that I envisaged in a recent article [Queen's Quarterly 68, 249 (1961)]. Writing on "Double standards and the university professor," I said the following: "To teach, even to teach well, is not by itself enough for the university professor. This has come to be accepted so widely and without question in top-ranking academic circles that it has assumed the proportions of sacred dogma. As with most dogmata, its very danger lies in its demand for blind faith. Such demands lead in turn to a very natural reaction-an ever-enlarging group is certain to appear sooner or later to challenge the dogma, or to cast it aside as untenable, or perhaps to replace it with a new and diametrically opposite one. Such a challenge seems to be looming in general attitudes toward the rôle of the university professor. As the pressure of increasing enrollments grows more and more acute, should we revise our concept of the ideal university teacher and adopt more firmly the tacitly accepted double standard of many inferior colleges?"

Needless to say I was surprised at the source of reaction. The difficulty stems not so much from the dichotomy in the responsibility of the professor but rather

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from double standards whereby certain endeavors are said to be desirable and yet do not appear to be rewarded. There is no evidence that much thought is ever given by those who exercise fiscal control of universities to any consideration other than the enhancement of the current and future standing and reputation of the specific institution involved. All evidence suggests that the quality of classroom teaching does not greatly alter the reputation of the modern university. We may be occasionally annoyed by this as individuals, but we must admit that it is generally true. The current, unspoken attitude is that a professor in

a university worthy of the name must devote a calculable fraction of his time to research or scholarship, whether he is drawn to these pursuits or not. If he refuses to conform, he will find advancement slow or lacking. If he conforms but is inept, his future is just as discouraging. Rarely-very rarely-he will be fired. Should he leave university teaching? Is he at fault, or is the "system"? How good a teacher must he be to compensate for obvious inadequacy in the other required facets of his profession?

The important ingredient for personal success in a university should be no

secret by this time. The aspect of the professor's efforts which enhances the university's reputation is not classroom teaching. Unfortunately, the ambivalent attitude of administrators toward teachers who do nothing but teach well has been confused by some with a lack of sympathy for good teaching (as contrasted, say, with profuse publication). The problem is confused further by the erroneous notion that the man who prides himself on being a teacher and nothing more is necessarily a good teacher. All of us in the universities have known some proud but tertible teachers, as well as others who were quite mediocre. Rare indeed is the really first-class university classroom teacher, and, in my experience, he is not likely to limit his interest to the dry, classroom aspect of his subject. I have often heard professors modestly deprecate their efforts in research, but I have never heard one deprecate his effectiveness as a teacher.

I would suggest that we must soon segregate from the main body of professors all those who wish to gratify their egos by teaching only, and those who wish to attain the same end by only doing research. The former should enter the public schools, high schools, technical schools, and junior colleges, where they are badly needed. The latter should seek employment in research laboratories within or without the university structure. Only those who can perform both functions of a professorship and who are anxious to do so should form the great mass of university staffs. Governing boards must stop equivocating in their policies.

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Universities must make clear to their teaching staffs, present and future, exactly what they conceive the role of the ideal professor to be. They must not beg questions such as those on the length of summer vacations, on what is considered to be true scholarship, and on what is a fair evaluation of teaching ability. They must stop paying fatuous lip service to "plain good teaching" and make clear that in a university it alone is not enough. They must end the callous pretence (aimed at an expedient increase of their teaching staffs in the approaching crisis of numbers) that it is enough. If they do not do these things, they will awaken one fine day to find that the reactionaries have effectively taken over.

J. V. BASMAJIAN

Anatomy Department, Queen's University, Kingston, Ontario, Canada





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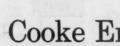
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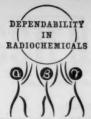


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# INDEX OF ADVERTISERS-10 November 1961

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American Electronic	London Co
Laboratories, Inc	Maryland Plastics, Inc
American Sterilizer Co	Matheson Coleman & Bell1479
Applied Physics Corp	Matheson Co
Applied Science Laboratories, Inc. 1580	Mettler Instrument Corp1460
Baker, J. T., Chemical Co	Millipore Filter Corp
Barnstead Still and Sterilizer Co 1534	Mnemotron Corp
Bausch & Lomb Inc. 1492	Nalge Co., Inc
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Bellco Glass Inc	Nester/Faust
Bethlehem Apparatus Co., Inc 1562	New Brunswick Scientific Co., Inc. 1475
Rrinkmann Instruments	New York Laboratory
Inc	Supply Co., Inc
Bronwill Scientific	Nikon Inc
Buchler Instruments, Inc. 1551	Nutritional Biochemicals Corp 1449
Canal Industrial Corp	Ohaus Scale Corp
Canner's Inc. 1580	Ohio Chemical & Surgical
Cenco Educational Films	Equipment Co
Charles River Mouse Farms 1580	Packard Instrument Co., Inc 1494
Chemical Rubber Co	Pennsylvania Scale Co
ChemTrac Corp	Perkin-Elmer Corp
Clay-Adams	Phoenix Precision Instrument Co 1490
Colorado Serum Co	Photovolt Corp
Cooke Engineering Co	Picker X-Ray Corp1456
Coors Porcelain Co	Pilot Chemicals, Inc
Corning Glass Works 1480	Pioneer Plastics
Cryogenic Engineering Co	Professional Tape Co., Inc 1557
Difco Laboratories	Radiochemical Centre1577
DuPont F I de Nomoure	Randolph Co
& Co., Inc	Raytheon Co
Eastman Kodak Co	Research Animals, Inc
Eaton-Dikeman Co	Sanborn Co
Edmund Scientific Co 1471	Sargent, E. H., & Co
Elgeet Optical Co	Schleicher, Carl, & Schuell Co 1575
Equipto	Schwarz BioResearch, Inc 1453
Erb & Gray Scientific, Inc 1474	Science Book Club
F & M Scientific Corp	Scientific Glass Apparatus Co., Inc. 1560
Gifford-Wood Co. 1538	Scientific Industries, Inc
Gilmont, Roger, Instruments, Inc. 1472	Scientific Products, Div. of
Gilson Medical Electronics 1450	American Hospital Supply Corp. 1470
Graf-Apsco Co	Sigma Chemical Co
Graphic Systems 1574	Sorvall, Ivan, Inc
	Standard Scientific Supply Corp. 1566
Greiner, Emil, Co	
Hamilton Co., Inc	Stoelting, C. H., Co
Hamner Electronics Co., Inc 1578	Stokes, F. J., Corp
Harford Metal Products	Taconic Farms
Harvard Apparatus Co., Inc 1545	Technicon Chromatography Corp 1577
Harvey-Wells Corp. 1454	Texas Instruments Inc
Heat Systems Co	Thermolyne Corp
Heller, Gerald K., Co	Tracerlab, Inc
Hitachi, Ltd	Trans-Sonics, Inc
Hormone Assay Laboratories, Inc. 1580	Tri-R Instruments
	U.S. Stoneware
Hospital Supply Co	
Hyland Laboratories	Unitron Instrument Co
Institute for Scientific Information 1542	Vanguard Instrument Co 1468
Instruments for Research	VirTis Co., Inc
and Industry	Waring Products Corp 1467
International Equipment Co 1461	Wild Heerbrugg Instruments, Inc. 1539
Isomet Corp	Wilkens Instrument & Research Inc. 1580
Johns-Manville	Will Corp
Kensington Scientific Corp 1558	Worthington Biochemical Corp 1569
Kirschner Manufacturing Co1551	Yellow Springs Instrument Co., Inc. 1575
Klett Manufacturing Co	Zeiss, Carl, Inc

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## CONTENTS

SCIENCE AND SOCIETY. 4 chapters

1

8 4

19

13

P

57

50

62

69

53

63

86

75

65

88

49

71

46

194

557

581

190 557

456 572 548

557

1485

1560

1562

1470

1553

1580

1577 1476

1554 1545

1572

1571

1568

1487

1468

1482

1467 1539

1580

1558

1569

1575

1464 OL. 134

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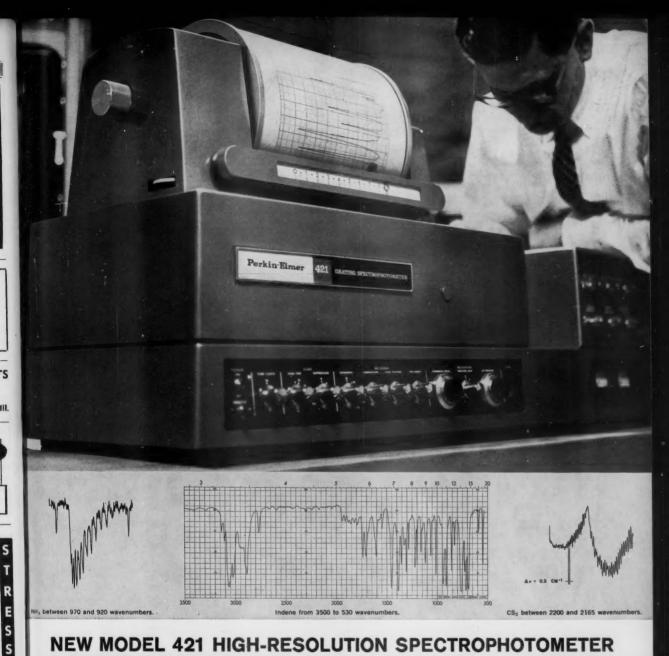
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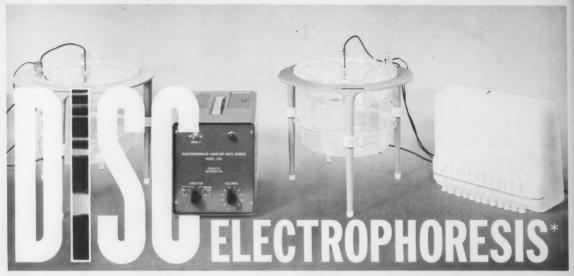
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